UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge

ZHP DEFENDANTS' RESPONSE TO PLAINTIFFS' STATEMENT OF UNDISPUTED MATERIAL FACTS IN SUPPORT OF PLAINTIFFS' MOTIONS FOR PARTIAL SUMMARY JUDGMENT

Defendants Zhejiang Huahai Pharmaceutical Co., Ltd.; Huahai U.S., Inc.; Prinston Pharmaceutical Inc.; and Solco Healthcare U.S., LLC (collectively, the "ZHP Defendants") submit this response to Plaintiffs' Statement of Undisputed Material Facts in Support of Plaintiffs' Motions for Partial Summary Judgment. (ECF 2569-3.)

ZHP and Its United States Subsidiaries Huahai US, Prinston, and Solco

1. Zhejiang Huahai Pharmaceutical Co., Ltd ("ZHP") is "[a] vertically integrated pharmaceutical manufacturer of API's and finished products," based in China, with "20 sub-branches/subdivisions located in USA, Shanghai, Hangzhou and Jiangsu, etc." ZHP's sales and marketing operations are based in China, New Jersey, and other locations around the world. ZHP also has three research and

development centers, two in China, and one in Cranbury, New Jersey. (ZHP-6 (Ex. 111); ZHP-7 (Ex. 112); ZHP-9 (Ex. 113)).[1]

ZHP Defs.' Response: Admitted with clarification that the number of "sub-branches/subdivisions" of ZHP referenced by Plaintiffs, as well as the number and location of its "research and development centers," have varied over time.

2. Jun Du was the Vice Chairman of the Board of Directors of ZHP. He also held the title of Executive Vice President of ZHP on an interim basis as necessary to attend audits by the FDA or European Union or EHS, when ZHP's Chairman Baohua Chen was unavailable, including in July and August 2018. (Jun Du 5/27/21 Dep. Tr. 25:13-34:24 (Ex. 1)).[2]

ZHP Defs.' Response: Denied in part. Mr. Du did not testify that it was "necessary" for him to be designated as "Executive Vice President" to attend the audits; rather, he simply testified that "I was only given this job responsibility when an audit conducted by either the FDA or the European Union or the EHS took place. (Jun Du 5/27/21 Dep. 33:21-24 (Pls.' SUMF Ex. 1).) In addition, the ZHP

[1] All exhibits in Plaintiffs' Statement of Undisputed Material Facts are attached to the Certification of Adam M. Slater in Support of Plaintiffs' Motion for Partial Summary Judgment.

[2] According to ZHP, Jun Du apparently retired sometime after sitting for his deposition in this case.

Defendants deny Plaintiffs' editorial comment in Footnote 2 regarding the timing of Mr. Du's retirement.

3. In addition to his executive positions with ZHP, Jun Du was the CEO of Huahai U.S., Inc., CEO of Prinston Pharmaceuticals, and CEO of Solco Healthcare. (Jun Du 5/27/21 Dep. Tr. 40:1-44:11, 49:3-9, 54:7-21).

ZHP Defs.' Response: Admitted.

4. Hai Wang, who testified as a 30(b)(6) corporate representative, is the President of Solco Healthcare, Senior Vice President of Prinston Pharmaceutical Inc., and Senior Vice President of Huahai US, Inc., and directly reported to Jun Du in all of his positions. (Hai Wang 3/10/21 Dep. Tr. 31:16-33:1, 34:7-12 (Ex. 2)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants generally admit the statements in Paragraph 4 but deny that Mr. Wang continues to hold these positions.

5. Huahai, U.S., Prinston, and Solco are wholly owned subsidiaries of ZHP. (ZHP Defs.' Answer (ECF 2549, ¶¶ 76-78)).

ZHP Defs.' Response: Denied in part. As will be clarified in the ZHP Defendants' forthcoming Amended Answer, neither Prinston nor Solco is wholly owned by ZHP. Solco is wholly owned by Prinston. Prinston is wholly owned by PrinJohnson Biopharm, Inc., of which ZHP owns approximately 93.5% through direct and indirect holdings.

6. Jun Du explained the relationship between ZHP's United States entities: "ZHP sells their API products directly in the U.S. market through Huahai U.S., including both the research and development APIs, as well as commercialized APIs." Prinston, "engages in the finished dose products, research and development, as well as the regulatory affairs of such products. It owns an ANDA of generic drugs." He described Solco as, "a company that sells the generic drugs of Prinston for which Prinston holds the ANDA." (Jun Du 5/27/21 Dep. Tr. 40:1-44:11, 49:3-9, 54:7-21).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that Mr. Du's cited testimony includes these statements, but Plaintiffs' transcription of one of the quotes above is incorrect, it should be: "It owns an ANDA . . . of generic drugs."

7. The valsartan DMF holder was ZHP and its US agent was Huahai US. (Hai Wang 3/10/21 Dep. Tr. 134:11-21). (*See, e.g.*, ZHP00079956 (Ex. 3); PRINSTON00012473 (Ex. 4)).

ZHP Defs.' Response: Admitted.

8. According to Hai Wang, "Prinston is the corporate of the pharmaceutical organization, it's the corporate body . . . Prinston pretty much does everything except the manufacture and except the marketing and sales as a pharmaceutical company. And the marketing and sales is through Solco . . . Solco is

the marketing arm for Prinston Pharmaceutical . . .” Hai Wang confirmed that Solco was a wholly owned subsidiary of ZHP. (Hai Wang 3/10/21 Dep. Tr. 45:13-21, 218:23-220:9).

ZHP Defs.’ Response: Denied in part. The ZHP Defendants admit that Mr. Wang’s cited testimony includes the quotes set forth in this paragraph, albeit in a different order than Plaintiffs have arranged them. However, Mr. Wang did not confirm that Solco was a wholly-owned subsidiary of ZHP. Mr. Wang merely testified “Yes” when asked “Do you see that?” after being read the statement “‘Solco is a fully owned subsidiary of Prinston Pharmaceutical, Inc.” from a document. (Hai Wang 3/10/21 Dep. 45:8-21 (Pls.’ SUMF Ex. 2).)

The Manufacture and Sale of valsartan

9. Valsartan is a generic drug known as an angiotensin receptor blocker (“ARB”), used for the treatment of high blood pressure, and other cardiovascular conditions. (ZHP Defs.’ Answer (ECF 2549, ¶¶ 263-64)).

ZHP Defs.’ Response: Admitted.

10. The brand name drug, or reference listed drug (“RLD”) for valsartan, is Diovan, and another version of the brand name drug is Exforge, which was a combination of valsartan and amlodipine (a calcium channel blocker). The brand drugs were sold by Novartis pursuant to an NDA in the United States. The approved forms of Diovan and Exforge did not include NDMA or NDEA impurities in any

regulatory or compendial document describing the approved formulation of those drugs. (ZHP01303141 (Ex. 5); ZHP02614594 (Ex. 6); PRINSTON00141349 (Ex. 101); https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html (Ex 8); Novartis, Novartis Pharmaceuticals Corporation (Novartis) Statement on Recall Outside the United States of Sandoz Generic valsartan and Sandoz valsartan and Hydrochlorothiazide Film-Coated Tablets (July 16, 2018) (stating: "The valsartan API (active pharmaceutical ingredient) in these products does not come from the same source as those products affected outside the United States. Patients in the United States currently taking Sandoz valsartan tablets, Sandoz valsartan and hydrochlorothiazide tablets, Sandoz amlodipine and valsartan tablets, Sandoz amlodipine, valsartan, hydrochlorothiazide tablets, Diovan®, Diovan HCT®, Exforge®, Exforge HCT® or Entresto® should continue to take their medication as directed by a physician."), https://www.novartis.com/us-en/news/novartis-pharmaceuticals-corporation-novartis-statement-recall-outside-united-states-sandoz-generic-valsartan-and-sandoz-valsartan-and-hydrochlorothiazide-film-coated-tablets (Ex. 9)).

ZHP Defs.' Response: Denied in Part. The ZHP Defendants admit the first two sentences of this paragraph. They also admit that the three USP monographs cited by Plaintiffs in this paragraph do not contain any references to NDMA or

NDEA under the various sections referring to valsartan and that the quote included from Exhibit 9 is correct.

However, the ZHP Defendants deny that "[t]he approved forms of Diovan and Exforge did not include NDMA or NDEA impurities" as a factual matter. In a June 2019 Citizen Petition, Valisure LLC and ValisureRX LLC reported a finding of NDMA in Novartis valsartan, which could only be a reference to branded Diovan because Novartis did not sell generic valsartan in the U.S. (June 13, 2019 Valisure Citizen Petition (Ex. 1 to Cert. of Jessica Davidson ("Davidson Cert.")).) Moreover, the limited materials cited by Plaintiffs do not establish that not one "regulatory or compendial document describing the approved formulation of those drugs" included NDMA or NDEA. Moreover, the FDA has recognized that "nitrosamines are common in water" (*see, e.g.*, September 1, 2020 FDA Statement (Davidson Cert. Ex. 2)), raising the possibility that manufacturing processes like Novartis's that use water (*see* U.S. Patent 5,399,578 (Novartis U.S. Valsartan Patent), at 15-33 (Davidson Cert. Ex. 3) (providing various ways to manufacture acyl compounds, including valsartan, using water), may include nitrosamines. That possibility may have become a reality here given Valisure's testing results. (June 13, 2019 Valisure Citizen Petition.)

10.5. ZHP manufactured the valsartan API at its Chuannan manufacturing facility using a series of manufacturing processes. One of the Deviation

Investigation Reports ("DIR's") prepared by ZHP and submitted to the FDA provides "Historical background information of valsartan manufacturing process." It explains, "There are three synthetic routes of valsartan in Huahai Chuannan Site, including TIN process, TEA process and $ZnCl_2$ process." ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797), beginning at 56 of 236 ("TEA DIR") (Ex. 10). According to Table 4-3, the "Summary of valsartan production history" at 62-63 of 236:

- The Tin process was utilized in Workshop 4 from October 2006 to March 2011, and in Workshop 2 from September 2010 to May 2014.
- The TEA process without sodium nitrite quenching was utilized in Workshop 4 from June 2008 to July 2011, and in Workshop 2 from December 2010 to May 2011.
- The TEA process with sodium nitrite quenching was utilized in Workshop 2 from May 2011 to May 2014, in Workshop W02 from May 2012 to March 2013, and in Workshop 4 from July 2011 to July 2015.
- The zinc chloride process was utilized in Workshop 2 beginning in November 2011 (no end date provided), and in Workshop W02 beginning in April 2012 (no end date provided).

These dates correspond to the dates provided in Table 4-1 at 57-58 of 236, providing the dates of process validation and registration.

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit the substance of this paragraph but note that the cited document does not show that it was submitted to the FDA.

11. Of note, following table 4-3, at 63 of 236, ZHP states that, "different manufacturing processes for valsartan may coexist in Workshop 2, Workshop 4 and Workshop W02." This created the potential for cross-contamination between drug product manufactured with the TEA with sodium nitrite quenching and zinc chloride processes.

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the cited document contains the quotation included above. However, they deny the second sentence because it is unsupported and inaccurately suggests that the ZHP defendants knew about or expected the potential for cross-contamination prior to the valsartan recall in 2018.

12. ZHP initially manufactured its valsartan API with what was referred to by ZHP as the valsartan TIN process. This process utilized tributyl tin chloride as a catalyst for Xylene, the solvent used in the crude step of the manufacturing process. Of note: "no dimethylamine and its derivative reagents were used. No nitrite was used for quenching after reaction. 2. Triethylamine hydrochloride is not used, and sodium nitrite is not used to quench. **No NDMA or NDEA impurities will be formed." ZHP's conclusion was that this process, which was the process utilized**

by the brand/RLD manufacturer Novartis for the manufacture of Diovan and Exforge, could not create NDMA or NDEA. (TEA DIR at 60-61, 68 of 236).[3]

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit the substance of this paragraph, with the following exceptions. First, as the TEA DIR shows, ZHP referred to the process at issue as the "Tin Process," not the "valsartan TIN process." (TEA DIR at 60 of 236 (Pls.' SUMF Ex. 10).) Second, "tributyl tin chloride" was not a catalyst for xylene; rather, "tributyl tin chloride" was used to catalyze the reaction of "valsartan intermediate 3" "with sodium azide in dimethylbenzene," for which xylene served as the solvent. (*Id*. at 60-61 of 236.) Third, while the ZHP Defendants admit that the cited document states, "No NDMA or NDEA impurities will be formed" in the "Tin Process," they deny that Diovan and Exforge were manufactured using this same process and also deny that these medications did not include NDMA or NDEA. In a June 2019 Citizen Petition, Valisure LLC and ValisureRX LLC reported a finding of NDMA in valsartan manufactured by Novartis, which could only be a reference to branded Diovan because Novartis did not sell generic valsartan in the U.S. (June 13, 2019 Valisure Citizen Petition.)

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[3] Although Plaintiffs use bolded text approximately 80 times in their SUMF, including when quoting from documents, the original text at issue was not bolded in the overwhelming majority of instances. The ZHP Defendants have only identified two instances in which the bolded language is included in the original text, both in Paragraph 48. (*Compare* ¶ 48, *with* ZHP01344159.)

13. In 2011, ZHP developed an alternative manufacturing process which it named TEA without sodium nitrite quenching, then the TEA process with sodium nitrite quenching, and yet another new process, the zinc chloride process which also included sodium nitrite quenching. The NDMA and NDEA impurities at issue were formed as a result of chemical reactions that involved the use of sodium nitrite for quenching, during the TEA with sodium nitrite quenching and zinc chloride processes. (Pages 57-62 in the TEA DIR).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit the substance of this paragraph, but deny any implicit suggestion that the ZHP Defendants knew about, or should have expected, the potential for NDMA and NDEA to form in the valsartan manufacturing processes that involved the use of sodium nitrite quenching.

The TEA With Sodium Nitrite Quenching Manufacturing Process

14. The root cause of the NDEA and NDMA impurities is set forth in the ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797) ("TEA DIR"). ZHP discussed the various pathways for the creation of NDEA in the TEA with sodium nitrite quenching process on page 50-55, and 61 of 236. ZHP established the three factors required to form NDEA in the final drug substance on 52 of 236:

- Presence of diethylamine in the manufacturing process, such as its presence in quenching step;

- Presence of nitrous acid in the manufacturing process, such as quenching of azide using sodium nitrite;
- The possibility of direct contact between secondary amines and nitrite in the presence of the target product.

Stated another way at 53 of 236: "Trace amount of diethylamine hydrochloride in triethylamine hydrochloride can react with nitrous acid (formed in situ between $NaNO_2$ and HCl) during the quenching of excess azide with sodium nitrite." ZHP's final valsartan DIR also conceded that based on a 2010 study from the Journal of Physical Chemistry, triethylamine could directly nitrosate with nitrous acid to form NDEA. (PRINSTON00761002-03 (Ex. 120)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit this paragraph to the extent it accurately quotes the TEA DIR. Similarly, they admit that Version 3 of DC_E-18003 (PRINSTON00076100) ("DC_E-18003 (v.3)") (Pls.' SUMF Ex. 120) references "*Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine Phys.Chem.A 2010, 114, 455-465*" and states that "[r]eaction of triethylamine with nitrous acid may also form NDEA without proceeding via the intermediacy of DEA." However, they deny the paragraph to the extent it reflects Plaintiffs' characterizations of the TEA DIR and DC_E-18003 (v.3). Specifically, the ZHP Defendants deny that they have conceded "that based on a 2010 study from the Journal of Physical Chemistry," the ZHP Defendants knew or should have expected that "triethylamine could directly

nitrosate with nitrous acid to form NDEA." Notably, Plaintiffs' own expert conceded that he was unfamiliar with this potential reaction before becoming involved in this litigation. (TPP Trial Defs.' SUMF Ex. 58, Najafi 2023 Dep. Vol. I 192:18-193:7; *see also id.* 193:8-15 (Dr. Najafi answering "yes" when asked if he learned of the reaction by which TEA could form NDEA "through [his] investigation in connection with this litigation").)

15. Min Li of ZHP, Vice-President for ZHP Analytical Operations and a 30(b)(6) corporate representative, started with ZHP in September 2014. He graduated from Johns Hopkins with a Ph.D in organic chemistry. (Min Li 4/20/21 Dep. Tr., 12:7-11, 23:19-24:2, 33:22-24 (Ex. 11)).

ZHP Defs.' Response: Admitted with clarification. Dr. Li's title is "Vice-President for Analytical Operations," not "ZHP Analytical Operations," as Plaintiffs assert. (Min Li 4/20/21 Dep. 12:7-11 (Pls.' SUMF Ex. 11).) And while the ZHP Defendants admit that Dr. Li earned a Ph.D. from Johns Hopkins in Organic/Bioorganic Chemistry, the cited transcript does not state that.

16. Dr. Li confirmed that the presence of NDEA resulted from the manufacturing process: "the DEA [diethylamine] is a typical process impurity of TEA, so DEA would also, yeah, would react with the nitrous acid to perform NDEA." He confirmed that the presence of NDMA resulted from the use of solvents containing the secondary amine impurities that were needed to form NDMA and

NDEA through the manufacturing process, as well as cross-contamination: "in some of the TEA raw material it may contain a trace amount of, you know, of dimethylamine, okay, so that's one root cause . . . for some of the, you know, product, they were manufactured, you know, using the share line, you know, with the zinc chloride valsartan." (Min Li 4/20/21 Dep. Tr. 77:8-80:16).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quotes contained in this paragraph are accurate excerpts from the cited deposition transcript but deny that Dr. Li "confirmed" how NDMA and NDEA formed in valsartan API. As a review of the entire deposition excerpt shows, Dr. Li was simply providing an overview of ***his*** understanding of the root cause of the formation of nitrosamines. (*See* Min Li 4/20/21 Dep. 77:21-23 ("The root cause, I think actually, based upon my understanding, they are slightly different.").) The ZHP Defendants also deny Plaintiffs' characterization of the cited testimony and the implicit suggestion that the ZHP Defendants knew or should have expected prior to the 2018 valsartan recall that NDEA would or could form during the TEA with sodium nitrite with quenching process.

17. The TEA DIR provides a detailed analysis of the causes of cross-contamination, including due to shared production lines and solvent recovery, at 126-135 of 236. With reference to cross-contamination due to shared production lines, the Report states in part on 129-130 of 236, "the residual NDMA and NDEA

in the equipment after cleaning for process switch were not analyzed . . . Based on the analysis of the NDMA and NDEA data, the original equipment cleaning procedure applied might not be able to get rid of the NDMA and NDEA residue on the equipment completely." On 138 of 236, the Report states: "no special cleaning and testing control were set in the process of cleaning focus on the trace amount of NDMA or NDEA impurity, it likely had trace amount of NDMA or NDEA impurity remaining in the equipment and resulted in carry-over into other grade of valsartan."

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quotes contained in this paragraph are accurate excerpts from the cited documents but deny Plaintiffs' characterization of the cited documents and the implicit suggestion that the ZHP Defendants knew or should have expected prior to the 2018 valsartan recall that: (1) NDEA would or could form during the TEA with sodium nitrite with quenching process; or (2) there was a risk of nitrosamine cross-contamination between the TEA with quenching and Zinc Chloride processes.

18. As stated in the TEA DIR, comparing the root cause for the formation of NDEA in the TEA with sodium nitrite quenching process to the root cause for the formation of NDMA in the zinc chloride process, "NDMA is generated by nitrosation reaction of the simultaneously presented dimethylformamide (containing degradation product/impurity dimethylamine) and nitrous acid; NDEA is similar to

NDMA in structure, and the formation mechanism is similar too, i.e., Nitrosation of diethylamine." (TEA DIR at 145 of 236).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quote contained in this paragraph is an accurate excerpt from the cited document but deny Plaintiffs' characterization of the cited document and the implicit suggestion that the ZHP Defendants knew or should have expected prior to the 2018 valsartan recall that NDEA and/or NDMA would form during the relevant valsartan manufacturing process.

The Zinc Chloride Process

19. In 2011, ZHP developed yet another alternative manufacturing process for its generic valsartan. ZHP changed certain substances used in the manufacturing process, including the substitution of the solvent dimethylformamide ("DMF") for trimethylamine, and zinc chloride for toluene in the tetrazole ring formation step, and increased the quantities of sodium azide and sodium nitrite. (ZHP01843066, ZHP 195 (Ex. 12)).

ZHP Defs.' Response: Admitted with clarification. As Plaintiffs' cited document makes clear, DMF was substituted for toluene, and zinc chloride was substituted for trimethylamine. (ZHP01843066, at 075 (Pls.' SUMF Ex. 12).) The ZHP Defendants admit the remainder of this paragraph.

20. During a meeting with an FDA investigator following the disclosure of the NDMA in the ZHP valsartan in June 2018, Jun Du stated that the increased production capacity and cheaper cost with the zinc chloride process change allowed ZHP to dominate the world market for valsartan. (PRINSTON00162373 (Ex. 13)).

ZHP Defs.' Response: Denied. The document cited by Plaintiffs states that "Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share." It makes no reference to "increased production capacity." Moreover, the testimony of at least one eyewitness explicitly contradicts this account. (*See* Dep. of Lihong (Linda) Lin (May 5, 2021), 208:21-209:5 (Davidson Cert. Ex. 4) (testifying "I do not recall Mr. Du saying this to the FDA" and that "the primary purpose of this change was to reduce impurity A in valsartan").)

21. The root cause of the zinc chloride process NDMA contamination is set forth in the ZHP Deviation Investigation Report dated July 20, 2018 (DC-18001, ZHP00004363-4471 (Ex. 14)) ("ZNCL DIR"), and is also discussed in the TEA DIR cited above. On page 17 of 33 of the ZNCL DIR, ZHP states, "Based on the previous mechanism analysis, this impurity is probably generated in the quenching process in which the product of the reaction is also present." On page 19 of 33, ZHP stated, "Based on the above elucidated root cause, the presence of trace amount of NDMA in the final valsartan API requires the convergence of the following three factors: i)

use of dimethylformamide (DMF) in the tetrazole formation step, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product." These are the same three factors described in the TEA DIR. This is further reiterated on page 22 of 33, including, "It seems clear that NDMA is only formed in Process II (Z[n]CL[$_2$]) associated with the use of solvent dimethylformamide (DMF) during the quenching of unreacted azide AND in the presence of the product of that step, indicating NDMA is a process impurity in Process II (ZNCL)."

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quotes contained in this paragraph are accurate excerpts from the cited documents with one exception,[4] but deny Plaintiffs' characterization of the cited documents and the implicit suggestion that the ZHP Defendants knew or should have expected prior to the 2018 valsartan recall that NDMA would or could form during the Zinc Chloride or TEA with quenching processes. Additionally, a comparison of the two referenced documents demonstrates that Plaintiffs' statement that "these are the same three factors described in the TEA DIR" is incorrect. The first factor described in the TEA DIR is "[p]resence of dimethylamine in the manufacturing process, such as its presence in tetrazole formation step," and there is no reference to "DMF." (*Compare* TEA DIR at 9 of 236, *with* ZNCL DIR at 19 of 33 (Pls.' SUMF Ex. 14).)

[4] The final quote in this paragraph contains three errors: Plaintiffs erroneously capitalized the "n" and "l" in "ZNCL" and failed to include a subscripted "2" after "ZNCL" in their quote from page 22 of 33 of the ZNCL DIR.

22. ZHP's test results show that some of ZHP's zinc chloride process valsartan was also cross-contaminated with NDEA, meaning those batches contained both NDMA and NDEA. (ZHP02364173 (Ex. 15)).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that the cited document indicates that some batches of valsartan produced with the Zinc Chloride process included both NDMA and NDEA, but deny Plaintiffs' assertion that the NDEA necessarily arrived there through cross-contamination given that the cited document only indicates the presence of NDEA and not its source.

23. Valsartan API manufactured with the zinc chloride process was utilized by the finished dose manufacturing arm of ZHP to manufacture finished dose product that ZHP then marketed and distributed in the United States through Prinston and Solco. (PRINSTON00000013-14, 00000016-17 (Ex. 63); PRINSTON00000023, 00000031-32 (Ex. 61)).

ZHP Defs.' Response: Admitted that valsartan API manufactured with the zinc chloride process was utilized by the finished dose manufacturing arm of ZHP to manufacture finished dose product. Denied that ZHP sold valsartan in the United States but admitted that Prinston d/b/a Solco marketed and distributed finished dose valsartan in the United States.

24. ZHP first sold valsartan via Prinston and Solco in the United States in October, 2015, "the first valsartan pills manufactured by ZHP and sold in the United States, the first time they were received was October 2, 2015." (Hai Wang 3/10/21 Dep. Tr. 96:8-97:8).

ZHP Defs.' Response: Denied that ZHP sold valsartan in the United States but admitted as to Prinston d/b/a/ Solco.

25. Prinston provided information to the FDA in connection with the recall notice which included the ANDA numbers of A204821 for valsartan and A206083 for valsartan/HCTZ, and the beginning and ending manufacturing dates of May 2015 to March 2018, and that Prinston first marketed valsartan on June 9, 2015 and valsartan-HCTZ on February 9, 2016. (Hai Wang 3/10/21 Dep. Tr. 205:28-266:14).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that the 60+ pages of Hai Wang's deposition transcript cited by Plaintiffs contain the information set forth above but deny any implicit suggestion that the statements in Paragraph 24 and Paragraph 25 here are inconsistent.

The NDMA/NDEA Contamination Levels in ZHP's valsartan

26. All of the valsartan sold by Prinston and Solco in the United States contained NDMA. The FDA was advised that "NDMA is present at a level greater than 0.5 ppm in all Huahai's drug substance batches for DMF 023491." (Hai Wang 3/10/21 Dep. Tr. 93:10-16, 154:3-16).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that: (1) Mr. Wang agreed with Plaintiffs' counsel's statement at his deposition that "[a]ll of the valsartan manufactured by ZHP and sold in the United States by Prinston and Solco contained the process impurity of NDMA" (Hai Wang 3/10/21 Dep. 93:10-16); and (2) the second quote is accurate. The ZHP Defendants deny Plaintiffs' implicit and unsupported assertion that "[a]ll of the valsartan sold by Prinston and Solco in the United States contained NDMA."

27. ZHP established that the NDMA levels in the API carried over to the levels in the finished dose because this was a process related impurity, "not a result of degradation of the product" and this information was provided by Prinston to the FDA. (Hai Wang 3/10/21 Dep. Tr. 116:22-118:23, 144:15-147:1, 152:8-12, 158:8-159:6).

ZHP Defs.' Response: Denied in part. The ZHP Defendants deny Plaintiffs' implicit and unsupported assertion that it has been "established" for purposes of this litigation that "the NDMA levels in the API carried over to the levels in the finished dose because this was a process related impurity, 'not a result of degradation of the product.'" However, the ZHP Defendants admit that Mr. Wang agreed at his deposition that: (1) "NDMA is an in-process impurity"; (2) ***ZHP*** assumed in 2018 "that the impurity levels in the API would carry to the finish[ed] dose formulation because it is a process impurity created in the manufacturing process" and "not a

result of degradation of the product"; and (3) this information was provided to the FDA. (Hai Wang 3/10/21 Dep. 146:18-147:1, 118:2-17.)

28. Minli Zhang, ZHP's Director of Finished Dose Formulation Quality, testified that ZHP, "compared the NDMA level in the API and the NDMA level in the finished dose products, and we found the results basically matched each other." (Minli Zhang Dep. 3/26/21 Dep. Tr., 509:15-17, 518:18-519:3, 521:8-19 (Ex. 16)). The relevant deviation investigation report states:

In order to qualify the impurity relationship between the dosage form and API, some batches of API and corresponding dosage form were choose at random to test this impurity by Quality Research Department (QR), the testing result is as below:

表 1：制剂成品及对应 API 批次检测结果列表

Table 1: testing result between dosage form batches and corresponding API

序号 SN	产品名称 Product Name	产品批号 Batch No.	产品规格 Strength (mg)	API 厂家批号 Vendor batch No. Of API	API 结果 Result for API	制剂结果 Result for dosage form
					NDMA 含量(ppm) Assay of NDMA (ppm)	
1.	缬沙坦片 USP Valsartan Tablets USP	341A18007	40	C5523-17-382	81.4	83.1
2.	缬沙坦片 USP Valsartan Tablets USP	342B17012	80	C5523-17-190	101.9	101.0
				C5523-17-191	101.7	
3.	缬沙坦片 USP Valsartan Tablets USP	343G17002	160	C5355-17-132	120.0	110.3
				C5355-17-133	104.5	
4.	缬沙坦片 USP Valsartan Tablets USP	344B17071	320	C5355-17-131	119.3	123.2
				C5355-17-132	120.0	
5.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	609B18003	80/25	D5191-16-133	3.4	2.9
6.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17003	320/25	D5191-16-027	27.7	31.3
7.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17007	320/25	D5191-15-149	7.9	6.4

从上表数据分析，制剂产品与 API 的检测结果的差值接近(0.5~9.7ppm)。

Based on analysis above, the testing difference value of API and dosage form is almost the same (0.5-9.7ppm)

(ZHP00683571, 683578 (Ex. 17)). ZHP determined that it was unnecessary to test any additional finished dose and used the API levels to determine the FD levels. (3/26/2021 Minli Zhang Dep. Tr., 520:22-523:19, 525:12-22 (discussing ZHP 189

(Ex. 18))). This holds true for both NDMA and NDEA: "According to the previous raw material investigation, i.e. presence of diethylamine impurities in triethylamine hydrochloride, combined with the formation mechanism of NDEA, it should be the nitrosation of diethylamine impurities (in triethylamine hydrochloride) by nitrite to produce NDEA impurities, which is carried over into crude products, and finally remain in valsartan finished products." (PRINSTON0075797, 75977 (Ex. 10)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quotes and images contained in this paragraph are correct excerpts of the cited material. They deny, however, Plaintiffs' unsupported assertion that Ms. Zhang's cited testimony establishes that "ZHP determined that it was unnecessary to test any additional finished dose and used the API levels to determine the FD levels" and their claim that "this holds true for both NDMA and NDEA." Ms. Zhang simply testified "[t]o the best of my recollection, that is correct" when asked if "aside from the testing that was conducted as part of the deviation investigation and the testing that may have been conducted as part of a method validation process at Xunqiao, you have not tested any other additional valsartan finished dose batches for NDMA." She did not offer any reasoning, nor does the quote from PRINSTON0075797. Accordingly, the ZHP Defendants deny Plaintiffs' unsupported characterization of Ms. Zhang's testimony and the cited document. Finally, the ZHP Defendants note that Ms. Zhang's CV simply states that at some point between September 2006 and

2015, she served as director of the "FDF QC laboratory," not Director of Finished Dose Formulation Quality. (Curriculum Vitae of Minli Zhang (Pls.' SUMF Ex. 52).)

29. Eric Gu confirmed the NDMA levels for the zinc chloride process as stated in a September 1, 2018 letter to the FDA. This included NDMA levels measured in various batches of 148.2, 158.8, 167.3, and 188.1 parts per million. (Eric Gu 4/6/21 Dep. Tr., 387:14-390:19 (Ex. 21)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the letter contained the stated measurements of NDMA, but the ZHP Defendants deny that Eric Gu "confirmed the NDMA levels for zinc chloride process as stated in a September 1, 2018 letter to the FDA." Dr. Gu simply testified "I see it" when counsel asked "[d]o you see that?" in reference to various portions of a document represented to be a September 1, 2018 letter to the FDA. (Eric Gu 4/6/21 Dep. 387:14-390:19 (Pls.' SUMF Ex. 21).) Further, the letter itself also shows that the overwhelming majority of batches had far lower concentrations of NDMA. (*See* ZHP, Response to DMF Information Request Letter, at 8 (Pls.' SUMF Ex. 23).) Further, as explained in the response to Paragraph 32, the document in question appears to have been sent to the FDA on September 2, 2018, not September 1, 2018.

30. Dr. Li confirmed that every batch of valsartan manufactured with the zinc chloride process exceeded the FDA limit of 96 nanograms. (Min Li 4/21/21 Dep. Tr., 306:15-23 (Ex. 22)).

ZHP Defs.' Response: Denied. The ZHP Defendants deny that "Dr. Li confirmed that every batch of valsartan manufactured with the zinc chloride process exceeded the FDA limit of 96 nanograms." Dr. Li simply testified "[y]eah, based upon, yeah, the results, yeah, that we tested, yes," when asked if "[e]very single batch manufactured with the zinc chloride process exceeded the FDA limit of 96 nanograms, correct?" Thus, Dr. Li testified that all the batches ZHP ***tested*** exceeded the FDA limit, not every batch manufactured. Additionally, as explained in the response to Paragraph 32, the document in question appears to have been sent to the FDA on September 2, 2018, and not September 1, 2018.

31. Dr. Li confirmed that ZHP's testing, documented in ZHP's September 1, 2018 Response to DMF Information Request Letter, showed that all 783 batches tested and listed in the document exceeded the limit set by the FDA, ranging up to 627 times the limit for NDMA. (Min Li 4/21/21 Dep. Tr. 472:12-476:19).

ZHP Defs.' Response: Denied. The ZHP Defendants deny that Dr. Li confirmed the material contained in ZHP's September 1, 2018 Response to DMF Information Request Letter. Instead, Dr. Li merely testified "[y]es" when asked by Plaintiffs' counsel "[l]ooking now at the batch numbered 518, we have 188.1 parts per million, which if you divide that by .3, that's 627 times the limit set by the FDA, correct?" Likewise, he testified, "[t]hey're all higher, yeah, than 0.3," when asked "783 batches. We can agree that all these tested batches tested at numbers many,

many times more than the limit the FDA ended up setting, correct?" In sum, Dr. Li did not confirm the accuracy of the material shown to him; he merely testified that Plaintiffs' counsel had correctly read from the document placed in front of him. Further, as explained in the ZHP Defendants' response to Paragraph 32, this response appears to have been sent to the FDA on September 2, 2018, and not September 1, 2018.

32. ZHP has documented the levels of NDMA and NDEA resulting from the at-issue manufacturing processes. ZHP's September 1, 2018 Response to DMF Information Request Letter (ZHP00079913 (Ex. 23)) includes Table 1, titled NDMA Test Results for Batches Manufactured Using the ZnCl Process at page 8 of 33. The table documents the results of testing of 783 batches, all containing NDMA well in excess of the 0.3 ppm level the FDA first adopted as an interim limit, and later adopted as a final limit for NDMA in valsartan. Table 2, titled NDMA Test Results for Batches Manufactured Using the TEA Process with sodium nitrite quenching at page 27-28 of 33 documents the results of testing of 55 batches, most containing NDMA and in each instance the NDMA level exceeds 0.3 ppm.

ZHP Defs.' Response: Denied in part. Exhibit 23 does not include the date of September 1, 2018. Moreover, a document identical to Exhibit 23 was submitted with a cover letter dated September 2, 2018. (*See* PRINSTON00012473 (Pls.' SUMF Ex. 4); PRINSTON00012480 (Davidson Cert. Ex. 5).) Thus, the cited

document is more accurately dated September 2, 2018. In addition, the cited document contains no information regarding the FDA's adoption of an interim or final limit for NDMA in valsartan of 0.3 ppm; however, the ZHP Defendants admit that the FDA set an interim and then final limit of 96 ng/day for NDMA, which converts to 0.3 ppm with respect to valsartan. Further, the ZHP Defendants admit that Table 1 in the cited document shows that the level of NDMA in all 783 tested batches exceeded 0.3 ppm, but deny Plaintiffs' imprecise characterization that the batches contained NDMA "well in excess of the 0.3 ppm" limit. Finally, the ZHP Defendants admit that Table 2 of the cited document shows that, of the 55 batches tested, NDMA was detected in only 46 of them, and that in each case, NDMA exceeded 0.3 ppm. The ZHP Defendants otherwise deny Plaintiffs' characterization of the document.

33. ZHP's Deviation Investigation Report, dated November 11, 2018, titled Investigation regarding unknown impurity (genotoxic impurity) of valsartan API (TEA process), documents NDEA levels for the TEA process with sodium nitrite quenching for valsartan API. (PRINSTON0075797 (Ex. 10)). Six validation batches had NDEA results of 0.03, 5.33, 12.77, 13.60, 18.83, and 13.51 ppm. (PRINSTON0075846). A separate table in that Report provides ranges and averages for the testing of 85 batches manufactured with the TEA process, documenting a range of 0.03-42.14, an average of 13.46 ppm. That table also shows NDEA levels

in 111 batches manufactured with the zinc chloride process, documenting a range of 0-4.23 and average of 0.18 ppm. (PRINSTON0075858). Thus, every batch was contaminated with NDMA, and many were also contaminated with NDEA, and every batch at issue contained NDMA and/or NDEA contamination in excess of the limits set by the FDA.

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit everything but the final sentence in this paragraph. The documents cited by Plaintiffs speak for themselves and reflect only the results of the testing of specific batches of valsartan API and finished product. Thus, the ZHP Defendants deny Plaintiffs' unsupported assertion that "every batch was contaminated with NDMA, and many were also contaminated with NDEA, and every batch at issue contained NDMA and/or NDEA contamination in excess of the limits set by the FDA."

34. ZHP's September 1, 2018 Response to DMF Information Request Letter provided to the FDA responds at page 29-30 of 33 to a question regarding a batch that was confirmed to have been manufactured with the TEA process with sodium nitrite quenching. **ZHP confirmed that the TEA process with sodium nitrite quenching was last used to manufacture valsartan API for the US market in July 2015**. This is consistent with the manufacturing dates per the TEA DIR cited above. Of note, ZHP's testing of this batch demonstrated NDMA contamination of 63.1 ppm, and ZHP stated that this could not be a process related

impurity due to the, "elucidated generation mechanism of NDMA," which was described only in the context of the zinc chloride process (use of DMF, impurity/degradant dimethylamine, reaction with nitrous acid, "during the subsequent quenching step in the presence of the product"). ZHP stated: "Probable contamination is suspected as source of this impurity in the TEA process, such as raw material, contamination due to shared production line etc., the investigation is ongoing." This is consistent with ZHP's recognition in the TEA DIR that there was cross-contamination due to shared production lines.

ZHP Defs.' Response: Denied in part. The ZHP Defendants deny the date ascribed to this document by Plaintiffs for the reasons explained in their response to Paragraph 32. The ZHP Defendants also deny that ZHP concluded in the document "that this could not be a process related impurity." Rather, as Plaintiffs correctly note, the document merely states that "[p]robable contamination is suspected as the source of this impurity [NDMA] in the TEA process." The ZHP Defendants otherwise admit this paragraph.

CEMAT And The July 27, 2017 Jinsheng Lin, Ph.D Email

35. CEMAT, which was wholly owned by ZHP and located in the ZHP Xunqiao site where the valsartan finished dose was manufactured, was created by ZHP to improve ZHP's capabilities in the identification of impurities in API and finished dose. (Min Li 4/20/21 Dep. Tr., 72:7-74:6).

ZHP Defs.' Response: Denied in part. The ZHP Defendants deny this paragraph to the extent Plaintiffs assert that CEMAT was created for the sole purpose of "improv[ing] ZHP's capabilities in the identif[ication] of impurities in API and finished dose." In the cited testimony, Plaintiffs' counsel asked Dr. Li about a document that stated that the "[m]ission of CEMAT [is t]o solve the most challenging technical problems encountered from research and development to scale up and manufacture of drug substances and finished products, particularly those related to process impurities, degradation products, and solid state and polymorphism." (Min Li 4/20/21 Dep. 74:7-75:23 (asking questions about ZHP00404315-327 (Davidson Cert. Ex. 6)).)

36. **The identification of impurities is, "part of the CGMP requirements."** (Min Li 4/20/21 Dep. Tr., 72:7-74:6).

ZHP Defs.' Response: Admitted with clarification. Although the ZHP Defendants admit that CGMP requirements require the identification of impurities, they do not require the identification of all impurities. ICH 3QA simply indicates manufacturers need not identify impurities in drugs with a maximum daily dose of 2 g or less where the impurity is equal to or less than 0.10% of the drug dose or 1.0 mg per day, whichever is less. (ICH Q3A (R2), Attachments 1 & 3, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-3-r2-impuritiesnew-drug-substances-step-5_en.pdf (ICH Q3a).) Thus, even with respect

to the minimum daily dose of valsartan of 40 mg (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283), a manufacturer would not be obligated to identify any impurity less than .04 mg, or 40,000 ng, of the medication. The only exception to this rule is for "those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold." (ICH Q3A at 4.) As previously stated, however, the ZHP Defendants deny they should have expected the presence of NDMA or NDEA in their valsartan API. (*See* TPP Trial Defs.' Omnibus SUMF, Ex. 64, "FDA Statement on FDA's ongoing investigation into valsartan impurities and recalls and an update on FDA's current findings" ("August 2018 Gottlieb Statement").) Thus, the exception in ICH Q3A would not apply. Moreover, as USP § 5.60.10 (Other Impurities in USP and NF Articles) makes clear, the "[t]presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater." (Pls.' SUMF Ex. 19, p. 4; Pls.' SUMF Ex. 20, p. 9.) This confirms that manufacturers are not required to identify all impurities. Indeed, the "USP Education" presentation by Dr. Ravi Ravichandran, Ph.D. cited by Plaintiffs is not to the contrary. (*See generally* Pls.' SUMF Ex. 65.)

37. The "Mission of CEMAT [is t]o solve the most challenging technical problems encountered from research and development to scale up and manufacture

of drug substances and finished products, particularly those related to process impurities, degradation products, and solid state and polymorphism." Dr. Li confirmed that "Process impurities would include, for example, the NDMA created by the zinc chloride process . . . And the creation of NDMA and NDEA in the TEA process with sodium nitrite quenching…." (Min Li 4/20/21 Dep. Tr., 74:17-76:10).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quotes contained in this paragraph are accurate excerpts of the cited testimony. However, the ZHP Defendants deny this paragraph to the extent Plaintiffs suggest Dr. Li testified as to the mission of CEMAT. Dr. Li merely stated "Mm-hmm, sure," when Plaintiffs' counsel asked "do you see that" after reading the excerpted text above. (Min Li 4/20/21 Dep. 74:17-76:10.) Further, the ZHP Defendants deny any suggestion or implication that CEMAT should have identified that the Zinc Chloride or TEA with quenching manufacturing processes could or would result in the formation of NDMA or NDEA prior to the discovery of this issue in 2018.

38. Jun Du confirmed that CEMAT, where the author of the email, Jinsheng Lin, Ph.D, was employed, conducted quality research including analytical methods for identification of impurities. (Jun Du 5/27/21 Dep. Tr. 101:8-18, 102:4-107:5).

ZHP Defs.' Response: Admitted.

39. A ZHP PowerPoint regarding CEMAT and the role of Jinsheng Lin, Ph.D, stated that Dr. Lin was in charge of the, "lab for process and degradation

impurity research," which was responsible, "to systematically design and conduct forced degradation research on drugs to research the mechanism of process impurity formation, to study the degradation pathway of the degradation impurities." Jun Du confirmed that the NDMA and NDEA impurities in the valsartan at issue were process impurities. (Jun Du 5/27/21 Dep. Tr. 116:11-120:5).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that Plaintiffs' counsel read aloud sections of a document that he represented to be a PowerPoint that related to CEMAT and that Dr. Li stated "that is correct" when asked if the document stated CEMAT was "the lab for process and degradation impurity research, and indicates that Jinsheng Lin, Ph.D., is in charge." (Jun Du 5/27/21 Dep. 118:8-12.) The ZHP Defendants also admit that Plaintiffs' counsel claimed to read the second quotation included in this paragraph from the document, which is in Chinese (*see* ZHP02557142 (Davidson Cert. Ex. 7)); however, counsel retracted the question before finishing (Jun Du 5/27/21 Dep. 116:3-7, 118:18-119:3 (asking about ZHP02557142)). With regard to the final sentence of Paragraph 39, Plaintiffs admit only that Mr. Du testified "that is correct" when asked, respectively, if "NDMA [was] a process impurity in valsartan" and if NDEA was a process impurity in the "TEA process with sodium quenching." (Jun Du 5/27/21 Dep. 120:5-15.) The ZHP Defendants otherwise deny Plaintiffs' characterization of Mr. Du's testimony and any suggestion that Jinsheng Lin was responsible for evaluating

impurities in valsartan API used in the recalled valsartan medications at issue in this litigation. Further, the ZHP Defendants deny any suggestion or implication that Dr. Lin or CEMAT should have identified that the Zinc Chloride or TEA with quenching manufacturing processes could or would result in the formation of NDMA or NDEA prior to the discovery of this issue in 2018.

40. Dr. Li testified to the contents of the July 27, 2017 email sent to him and others within ZHP by Jinsheng Lin, Ph.D, who worked at CEMAT. The email explicitly documented that it was known at that time that ZHP's valsartan API contained NDMA, which occurred due to the quenching with sodium nitrite, and that this was a "common problem in the production and synthesis of sartan APIs." The email also confirmed that the presence of nitrosamines would create, "an extremely high GMP risk." (Min Li 4/20/21 Dep. Tr., 82:11-83:7, 85:7-86:2, 86:6-14, 87:19-88:7, 88:13-90:2, 90:7-10, 90:14-23). To be complete, Dr. Li reviewed the Chinese version of the email and confirmed that the email stated the following:

> Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO compound; **it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic.**
>
> * * *
>
> **If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be**

> **an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended** to improve other quenching processes (such as NaClO) along with **the optimization of the valsartan sodium azide quenching process.**
>
> * * *
>
> I've also attached a patent of a 2013 sodium azide NaClO quenching method by Zhejiang Second Pharma Co., Limited. They proposed that the use of NaNO2 quenching will result in the formation of N-NO impurities. At the same time, they used ZHP's crude valsartan in their LC-MS test and detected this impurity. **This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue.**

(Min Li 4/20/2021 Dep. 82:11-12, 87:19-88:7, 88:13-89:18 (discussing ZHP-295 (Ex. 109)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that: (1) Jinsheng Lin, Ph.D., who worked at CEMAT, sent a group of employees an email on July 27, 2017; and (2) the email referenced a possible GMP risk for irbesartan. They further admit that Dr. Li responded with various affirmative statements when counsel read each of the paragraphs above in English and asked if they were consistent with the Chinese version in front of Dr. Li. (Min Li 4/20/2021 Dep. 87:19-88:7, 88:13-89:18.)

The ZHP Defendants deny the remainder of the paragraph, including Plaintiffs' assertions regarding the meaning and legal significance of Dr. Lin's July 27, 2017 email. Specifically, the ZHP Defendants deny that the July 27, 2017 email

"explicitly documented that it was known at that time that ZHP's valsartan API contained NDMA, which occurred due to the quenching with sodium nitrite, and that this was a 'common problem in the production and synthesis of sartan APIs.'" As ZHP's corporate representative, Jucai Ge, explained at her deposition, the July 27, 2017 email does not address valsartan API. Instead, the email refers to a potential impurity in irbesartan, a different drug molecule, and compares it to an impurity known as Impurity K that is associated with deacylated valsartan, yet another drug molecule. According to Ms. Ge, "if you look into the context of this e-mail, you can tell that at that time [Dr. Lin] was trying to make a comparison between NDMA and Impurity K and the impurity found in the technical improvement of irbesartan, since they were all nitroso compounds, and he was merely trying to make a toxicology comparison." (Jucai Ge 5/26/22 Dep. 92:8-15 (Pls.' SUMF Ex. 30).) Ms. Ge also clarified that "[p]rior to June 2018, [the ZHP Defendants] were not aware of the . . . existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process." (*Id.* 82:6-12.)

40. ZHP subsequently confirmed that its irbesartan was contaminated with NDEA due to its use of triethylamine and sodium nitrite quenching in the manufacturing process. (ZHP00367403, 367435-36 (Ex. 110)).

ZHP Defs.' Response: Admitted with clarification. The cited document, which is dated months after the valsartan recall, merely states that "[a]ccording to

the current investigation, the possible sources of NDEA impurity residue in Irbesartan products are as follows: In the Crude process of Irbesartan, TEA and DEA which contains in triethylamine hydrochloride reacts with sodium nitrite which residue in sodium azide to form NDEA impurities." (ZHP00367403, at 435-36 (Pls.' SUMF Ex. 110).)

41. Mr. Du confirmed the substance of the July 27, 2017 email, including that the impurity seen in the irbesartan was likely an N-NO compound, and that, "**it was similar to the NDMA from the sodium nitrite quenching in valsartan.**" (Jun Du 5/27/21 Dep. Tr. 107:12-115:23).

ZHP Defs.' Response: Denied. Mr. Du did not confirm the substance of the July 27, 2017 email, but instead responded to a series of deposition questions regarding whether the document said certain things. For example, Plaintiffs' counsel asked whether, in the email, "Dr. Lin indicates, 'It is similar to the n-nitroso-dimethylamine that occurs in valsartan when quenched with sodium nitrite." (Jun Du 5/27/21 Dep. 110:14-17.) In response, Mr. Du stated: "[n]o, it did not say so. Rather, it said it was similar to the NDMA from the sodium nitrite quenching in valsartan." (*Id.* 110:18-21.) Moreover, there are multiple ways to translate the document and there is a dispute as to what the July 27, 2017 email says and its meaning. (*See* Pls.' SUMF Ex. 24, at 7 (alternate translation of July 27, 2017 email stating: "it is probably that it is the N-NO compound, similar to the N-

nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite").) Further, as noted above, Jucai Ge testified that "[p]rior to June 2018, [the ZHP Defendants] were not aware of . . . the existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process." (Jucai Ge 5/26/22 Dep. 82:6-12.)

41.5. ZHP did not disclose its knowledge of and about the NDMA contamination of its valsartan to the FDA at the time of the July 27, 2017 email. (Min Li 4/20/21 Dep. Tr., 177:11-178:4, 178:19-179:1). In fact, ZHP did not disclose the contamination at all before the disclosure in June 2018. (PRINSTON00000001 (Ex. 80)).

ZHP Defs.' Response: Denied. "Prior to June 2018, [the ZHP Defendants] were not aware of . . . the existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process." (Jucai Ge 5/26/22 Dep. 82:6-12.) And when "Huahai found a presence of N-nitrosodimethylamine (NDMA) in Huahai's valsartan API during their evaluation of the API quality to a potential customer" in June 2018 (PRINSTON00000001 (Pls.' SUMF Ex. 80); ZHP01875818 (Defs.' SUMF Ex. 42), Prinston reported it to the FDA within a week. (PRINSTON00000001.)

42. The translation of the July 27, 2017 email provided and used by ZHP during depositions is consistent with the testimony of ZHP's corporate

representatives, and also clearly states that there was NDMA in ZHP's valsartan. (Ex. 24).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that Ex. 24 referenced in Paragraph 42 is a translation provided by the ZHP Defendants and that it contains the phrase "similar to the N- nitrosodimethylamine group produced by the quenching of valsartan with sodium nitrite." They otherwise deny the paragraph. As Jucai Ge explained, "if you look into the context of [the July 27, 2017] e-mail, you can tell that at that time [Dr. Lin] was trying to make a comparison between NDMA and Impurity K and the impurity found in the technical improvement of irbesartan, since they were all nitroso compounds, and he was merely trying to make a toxicology comparison." (Jucai Ge 5/26/22 Dep. 92:8-15.)

42.5 Plaintiffs' original translation was confirmed by Min Li and is attached as Exhibit 108.

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that Plaintiffs' English translation of Dr. Lin's July 27, 2017 email that was shown to Dr. Li at his deposition is attached to Plaintiffs' Statement of Undisputed Material Facts as Exhibit 108. They further admit that Dr. Li responded with various affirmative statements when counsel read portions of that English translation aloud and asked if they were consistent with the Chinese version in front of Dr. Li. (Min Li 4/20/2021 Dep. 87:19-88:7, 88:13-89:18.) The ZHP Defendants deny that Dr. Li

"confirmed" Plaintiffs' translation or that Dr. Li's statements regarding Plaintiffs' translation of Dr. Lin's July 27, 2017 email have legal significance.

CGMP Violations and Adulteration of ZHP's valsartan:
The FDA Investigation and Findings

43. Following ZHP's disclosure of the NDMA impurity to the FDA, the FDA initiated an investigation. On July 23-August 3, 2018 FDA performed a foreign comprehensive "For Cause" inspection of the API manufacturing site located at Chuannan, Linhai, Taizhour, Zhejiang.

ZHP Defs.' Response: Admitted with clarification. Although Plaintiffs provide no support for this paragraph, the ZHP Defendants admit that the FDA performed a "for cause" inspection of the API manufacturing site located at Chuannan, Linhai, Taizhou, Zhejiang from July 23 to August 3, 2018, following ZHP's disclosure of the NDMA impurity to the FDA.

44. Eleven (11) observations were cited on Form FDA 483, Inspectional Observations, date issued August 3, 2018. (ZHP00061069-79 (Ex. 25)). The observations included:

> QUALITY SYSTEM
> OBSERVATION 1
> The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs)is not adequate. Specifically,
> a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or APIs.

Critical Change Request PCRC-11025 was initiated November 27, 2011 and closed November 29, 2011, for the stated purpose of making changes to the valsartan manufacturing process to reduce the current conversion rate (60% - 70%) of the known isomer impurity D-valsartan in the final API and increase batch yields (current batch yield 400 - 500 Kg per batch).

i) you did not conduct and document a formal risk assessment for Change Request PCRC-1 1025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API for this critical change to your validated manufacturing process prior to your quality unit approving the change.

ii) you hired an outside laboratory to conduct a small lab scale research project. Based on the results of a lab scale research project you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches. Your Deputy Director of Manufacturing stated you have commercial experience and since you only changed the catalyst and the solvent there was no need to conduct pilot scale trial batches before instituting critical changes on a commercial scale.

You initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs. You do not have a quality agreement with the outside laboratory you used to perform a lab scale research project requiring (prior to initiating testing and reporting results): qualification of all instruments used to conduct tests; validation of all software used with qualified instruments to conduct tests; calibration of all applicable measurement devices against traceable standards prior to use; use of official standards as appropriate; if applicable, establishing system suitability prior to testing samples and processing data; and validation of all test methods used for testing.

b) **you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.**

i) You did not identify specific parameters and specify acceptance criteria for those parameters prior to implementing changes, as part of critical Change Request PCRC-11025, to use to evaluate if the implemented changes decreased the isomer conversion of D-valsartan and increased the batch yield.

ii) Additional testing requirements associated with critical changes are not always based on sound scientific judgement. Change Request PCRC-11025 included changing both the catalyst and the solvent in your validated manufacturing process. Additional testing requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on three batches a year.

c) **you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process.** You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File valsartan USP (Process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

d) written change control procedures should provide for the identification, documentation, appropriate review, and

approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Your quality unit does not always follow your written procedure for change control. Your written procedure Change Control System SMP-018.05 effective December 30, 2017 section 5.3.6 (3) specifies QA shall reject the change if the action cannot meet predetermined expectations. Critical Change Request PCRC-11025 did not include acceptance criteria with predetermined expectations. valsartan Product Development Report-01 dated April 13, 2012 Table 8 includes D-valsartan isomer impurity (specification < 1.0%) from three batches manufactured according to the validated manufacturing process (results range from 0.46% - 0.57%) and Table 10 includes D-valsartan isomer impurity from the three validation batches manufactured using a different catalyst and solvent (results range from 0.38% - 0.40%). The product development report is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. valsartan Product Development Report-01 did not compare the batch weights from batches manufactured immediately before the change to the validated manufacturing process and the first batches manufactured after implementing changes to the manufacturing process.

* * *

OBSERVATION 3

The system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated. Specifically,

* * *

b) major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for valsartan batches D5191-17-023 and D5191-17-024 with OOS results for a single unknown impurity (specification < 0.10%). You confirmed OOS results for valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38%.

i) you did not identify a root cause for the single unknown impurity results in batches D5191-17-023 and D5191-17-024. You stated the root cause was probably due to occasional fluctuation in your manufacturing process. You did not attempt to identify this single unknown impurity. You did not attempt to identify the source of fluctuations in your manufacturing process for valsartan.

ii) you did not develop an adequate Corrective Action and Preventive Action (CAPA) plan. The CAPA you listed on Deviation Investigation Report Form for Deviation DDW02-17003 included: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs. You did not review your manufacturing process and manufacturing batch records to determine if your manufacturing process and manufacturing batch records could be revised to reduce process variation. You did not interview employees to determine if employees consistently and reproducibly follow your manufacturing instructions.

iii) you did not conduct a thorough risk assessment. Your risk assessment consisted of answering 26 generic questions: yes, no, or NA (Not Applicable). Deviation DDW02-17003 investigation did not include documentation showing a more thorough risk assessment was conducted by your risk management team. Your written procedure for Quality Risk Management SMP-023.03 effective November 1, 2017 section 7.1.3 specifies a risk management team should be established when solving major risk issues, and section 7.1.5 of the same

procedure specifies to select different tools according to the risk category. Quality Risk Management SMP-023.03 section 8.3 specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not specify which risk management methods and tools to use in association with specific deviation categories.

c) you do not always thoroughly document investigations. your written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018 section 6.4.2 specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP~17.04 effective May 30, 2016). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

d) you do not always thoroughly investigate deviations before closing the deviation. Deviation was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification <0.50%) valsartan intermediate condensate HC] batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%). The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in process impurity observed in other batches but at levels not more than 0.10%. You did not identify a root cause.

Your corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity. You did not develop a preventive action plan. You did not identify the single unknown impurity. You reprocessed valsartan intermediate condensate HC] batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17024M. You then closed the investigation without identifying the single unknown impurity.

> e) you do not always follow your written procedures. Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature. You classified Return No. RC-18006 as not quality related for valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD specifications, a physical feature. The Treatment Record section and closure date on Return No. RC-18006 were left blank.

(*Id.* at 1-3, 5-7) (emphasis added).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit only that this paragraph accurately quotes from the Investigational Observations, although the original is not bolded.

45. In a letter from the FDA to Mr. Du dated September 21, 2018, which enclosed the Form FDA 483, the FDA stated the July 23-August 3, 2018 inspection resulted in an "Official Action Indicated" (OAI) inspection classification, and that **the facility was "considered to be in an unacceptable state of compliance with regards to CGMP**." (ZHP00061068 (Ex. 26)).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit this paragraph only to the extent that it accurately quotes the cited document.

46. On September 28, 2018, FDA issued a letter to Mr. Du of ZHP, informing him that ZHP had been placed on the Import Alert list (Import Alert 66-40) and that **future shipments were subject to refusal of admission to the United**

Sta**tes until ZHP could demonstrate their products were in cGMP compliance.** (ZHP00061080 (Ex. 27).

ZHP Defs.' Response: Admitted with clarification. The document cited by Plaintiffs states that "all future shipments of drugs that originate from your facility ***may*** be refused admission into the United States (U.S.) until your firm can demonstrate the drugs manufactured at this site, and intended for the U.S. market, are in compliance with CGMP." (ZHP00061080 (Pls.' SUMF Ex. 27) (emphasis added).)

47. On November 29, 2018, the FDA issued a Warning Letter (320-19-04) to ZHP notifying ZHP of significant deviations from cGMPs for their API manufacturing operations, and stating that the API was consequently adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 U.S.C. 351(a)(2)(B).

ZHP Defs.' Response: Denied in part. The ZHP Defendants deny any suggestion that the warning letter constituted a final regulatory determination that ZHP's API was adulterated. (*See* FDA, Regulatory Procedures Manual § 4-1-1, at 4 (June 2022), https://www.fda.gov/media/71878/download ("A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action. For these reasons, FDA does not consider Warning Letters to be final agency action on which it can be sued.").)

48. The FDA Warning Letter catalogued a number of cGMP violations directly tied to the manufacture of the contaminated ZHP valsartan. This included:

> **1. Failure of your quality unit to ensure that quality-related complaints are investigated and resolved.**
>
> *valsartan API*
>
> Your firm received a complaint from a customer on June 6, 2018, after an unknown peak was detected during residual solvents testing for valsartan API manufactured at your facility. **The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA).** Your investigation (DCe-18001) determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing process (referred to as the process in your investigation) was impacted by the presence of NDMA. However, FDA analyses of samples of your API, and finished drug product manufactured with your API, identified NDMA in multiple batches manufactured with a different process, namely the triethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers. Your investigation also failed:
>
> - To include other factors that may have contributed to the presence of NDMA. For example, your investigation lacked a comprehensive evaluation of all raw materials used during manufacturing, including potable water.
>
> - To assess factors that could put your API at risk for NDMA cross-contamination, including batch blending,

solvent recovery and re-use, shared production lines, and cleaning procedures.

- To evaluate the potential for other mutagenic impurities to form in your products.

Our investigators also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms. For example, valsartan intermediates (C20213-17-339 and C20213-17-340) failed testing for an unknown impurity (specification < 0.5%) with results of 0.56% for both batches. Your action plan indicated that the impurity would be identified as part of the investigation; however, you failed to do this. In addition, no root cause was determined for the presence of the unknown impurity. You stated that you reprocessed the batches and released them for further production.

Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was suspected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further. Additionally, residual solvent chromatograms for valsartan API validation batches manufactured using your ZnCl2 process, with DMF in 2012 (C5355-12-001, C5355-12-002, and C5355-12-003) show at least one unidentified peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute.

Your response also states that you were not the only firm to identify NDMA in valsartan API. In your case, FDA analyses of samples identified amounts of NDMA in valsartan API manufactured at your firm that were significantly higher than the NDMA levels in valsartan API manufactured by other firms. FDA has grave concerns about the potential presence of mutagenic impurities in all

intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation.

* * *

2. Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API.

In November 2011 you approved a valsartan API process change (PCRC - 11025) that included the use of the solvent DMF. **Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine**. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility.

You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change. You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients.

Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and

> **that that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce.**
>
> Your response does not describe sufficient corrective actions to ensure that your firm has adequate change management procedures in place: (1) to thoroughly evaluate your API manufacturing processes, including changes to those processes; and (2) to detect any unsafe impurities, including potentially mutagenic impurities. For FDA's current thinking on control of potentially mutagenic impurities, see FDA's guidance document M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk for approaches that FDA considers appropriate for evaluating mutagenic impurities, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf.

(ZHP01344159 (Ex. 28)) (emphasis added). The Letter also stated: "Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance," and "You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations." (*Id.* at 5).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that this paragraph accurately quotes Warning Letter T320-19-04. But see response to Paragraph 47.

49. The November 29, 2018 Warning Letter was written in response to the August 26, 2018 letter to the FDA signed by Jun Du, which was ZHP's response to the 483 notification issued August 3, 2018. The FDA stated in part: "**This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API)," including**, "**Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API**." (Jun Du 5/28/21 Dep. Tr. 234:13-237:16 (Ex. 29)).

ZHP Defs.' Response: Admitted with clarification. This paragraph accurately quotes from Warning Letter 320-19-04. But see response to Paragraph 47.

50. Jun Du acknowledged that The Warning Letter listed a number of CGMP violations, including: "you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine," and, "**You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately [detected and] controlled in your valsartan API before you approved the process change**. **You are responsible for developing and using suitable methods to detect impurities**

when developing, and making changes to your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." (Jun Du 5/28/21 Dep. Tr. 237:18-243:20).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that Warning Letter 320-19-04 contains the quoted material with the corrections bracketed in red above. (*See generally* ZHP01344159 (Pls.' SUMF Ex. 28).) They also admit that Mr. Du acknowledged that Plaintiffs' counsel read correctly from the letter. (Jun Du 5/28/21 Dep. 237:18-243:20 (Pls.' SUMF Ex. 29).) But see response to paragraph 47. In addition, the ZHP Defendants note that Dr. Scott Gottlieb stated in an August 2018 statement that "NDMA's properties make it difficult to find," and that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it." (TPP Trial Defs.' Omnibus SUMF, Ex. 64, August 2018 Gottlieb Statement at 4.)

51. The Warning Letter directly rejected ZHP's position set forth in the August 26, 2018 letter signed by Mr. Du, in response to the 483 notification, that it could not have been expected to identify the nitrosamine impurities. The FDA stated, "**Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry**

practice and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce." **Mr. Du agreed that ZHP was responsible for the quality of the drugs produced by ZHP**. (Jun Du 5/28/21 Dep. Tr. 247:17250:22).

ZHP Defs.' Response: Partially denied. The ZHP Defendants admit that Mr. Du stated at deposition that Warning Letter 320-19-04 contains the quoted material above and that ZHP is responsible for the quality of the drugs it produces. (Jun Du 5/28/21 Dep. 247:17-250:22.) However, the ZHP Defendants deny any suggestion that the quotes above mean that ZHP knew or should have expected that nitrosamines would form during the valsartan API manufacturing process or that they performed inadequate risk assessments. Moreover, Dr. Scott Gottlieb, the FDA Commissioner, in a statement dated August 30, 2018, stated: "Before [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process." (August 2018 Gottlieb Statement at 4.) Also see response to paragraph 47.

52. This is consistent with the USP requirement that nonmonograph tests must be utilized to detect impurities that result from a change in manufacturing process if its presence is inconsistent with good manufacturing practices or good pharmaceutical practices:

> Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with good manufacturing practices or good pharmaceutical practices.

(Ex. 19, p. 4; Ex. 20, p. 9). Put differently, USP requires manufacturers to characterize their products' impurity profiles, including by conducting a "sound scientific appraisal of the chemical reactions involved in the synthesis of the drug substance[.]" (Ex. 66, p. 2). And when they modify the manufacturing process they are required to identify all impurities, via whatever analytical method is necessary to do so. (Ex. 65, p. 18, 53). The monographs for valsartan USP did not contain a test or limit for NDMA or NDEA. (ZHP01303141 (EX5); ZHP02614594 (Ex. 6); PRINSTON00141349 (Ex. 101)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the cited materials contain the quotes set forth above and that three monographs for valsartan USP cited by Plaintiffs did not contain a test or limit for NDMA or NDEA. They deny the remainder of the paragraph.

First, the USP's requirement that "[n]onmonograph tests and acceptance criteria suitable for detecting and controlling impurities . . . should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with good manufacturing practices or good pharmaceutical

practices" implicitly requires that the manufacturer recognize or know that there is a risk of a specific impurity. Otherwise, it would be impossible for a manufacturer to know whether the presence of such a potential impurity is "inconsistent with good manufacturing practices or good pharmaceutical practices." (Pls.' SUMF Ex. 19, p. 4; Pls.' SUMF Ex. 20, p. 9.) Because the ZHP Defendants deny that they knew or should have expected the presence of NDMA and NDEA in their valsartan API, they deny that this USP requirement was applicable. (*See* August 2018 Gottlieb Statement at 4 (stating "NDMA's properties make it difficult to find," that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it," and that "[b]efore [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process").

Second, the ZHP Defendants deny that "when [manufacturers] modify the manufacturing process they are required to identify all impurities, via whatever analytical method is necessary to do so." As an initial matter, ICH 3QA indicates manufacturers need not identify impurities in drugs with a maximum daily dose of 2 g or less where the impurity is equal to or less than 0.10% of the drug dose or 1.0 mg per day, whichever is less. (ICH Q3A (R2), Attachments 1 & 3, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-3-r2-

impuritiesnew-drug-substances-step-5_en.pdf (ICH Q3a).) Thus, even with respect to the minimum daily dose of valsartan of 40 mg (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021283), a manufacturer would not be obligated to identify any impurity less than .04 mg, or 40,000 ng, of the medication. The only exception to this rule is for "those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold." (ICH Q3A at 4.) As previously stated, however, the ZHP Defendants deny they should have expected the presence of NDMA or NDEA in their valsartan API. (*See* August 2018 Gottlieb Statement.) Thus, the exception in ICH Q3A does not apply. Moreover, as USP § 5.60.10 (Other Impurities in *USP* and *NF* Articles) makes clear, the "[t]presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater." (Ex. 19, p. 4; Ex. 20, p. 9.) This confirms that manufacturers are not required to identify *all* impurities. Indeed, the "USP Education" presentation by Dr. Ravi Ravichandran, Ph.D. cited by Plaintiffs is not to the contrary. (*See generally* Pls.' SUMF Ex. 65.)

53. Mr. Du confirmed that the FDA placed ZHP on Import Alert on September 28, 2018, and that, "This import ban stopped the manufacturing of API

products at our Chuannan facility. Not limited to valsartan. That's a decision made by the FDA." (Jun Du 5/28/21 Dep. Tr. 251:2-15).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that Mr. Du testified that the "import ban stopped the manufacturing of API products at our Chuannan facility. Not limited to valsartan. That's a decision made by the FDA." An import alert, however, does not require a manufacturer to stop production; rather, an import alert has the effect of, among other things, "plac[ing] the responsibility back on the importer to ensure that the products being imported into the United States are in compliance with the FDA's laws and regulations." (FDA: Import Alerts, https://www.fda.gov/industry/actions-enforcement/import-alerts.) Thus, the ZHP Defendants deny this paragraph to the extent Plaintiffs assert that Import Alert 66-40 ***required*** the ZHP Defendants to stop the manufacturing of API products at the Chuannan facility. They otherwise admit the paragraph.

54. Jucai Ge, ZHP's Quality Assurance Director, API Division **confirmed that when the FDA informed ZHP that its valsartan was adulterated, "That means that in our manufacturing process, our methods, facilities, and controls did not conform to cGMP."** (Jucai Ge 5/26/22 Dep. Tr. 26:10-29:5 (Ex. 30)).

ZHP Defs.' Response: Denied. Ms. Ge merely testified about the FDA definition of adulterated, and did not state that she, or the ZHP Defendants, agree that the ZHP Defendants violated CGMPs. As explained later in Ms. Ge's testimony,

"from [ZHP]'s point of view, we have always . . . conformed to GMP or in compliance with GMP," which was a position "reflected in [ZHP]'s response to FDA's warning letter, as well as the communications with FDA over a long period of time." (5/26/22 Jucai Ge Dep. 29:21-31:3.) Also see response to Paragraph 47.

ZHP'S Admissions Regarding Violations of cGMPs

55. Eric Gu, a 30(b)(6) corporate representative, was the President/General Manager of Shanghai Syncores since February, 2014. The function of Shanghai Syncores, which was a wholly owned subsidiary owned by ZHP and based in ZHP's finished dose manufacturing facility as set forth above, is described in a PowerPoint dated in July, 2013, as "[p]rovid[ing] world-class R&D and manufacturing services to global pharmaceutical and biotechnology companies." (Eric Gu 4/5/21 Dep. Tr., 49:17-56:3 (Ex. 31); ZHP 225, p. 16 (Ex. 90)).

ZHP Defs.' Response: Denied in part. None of the cited evidence supports that Shanghai Syncores is "based in ZHP's finished dose manufacturing facility." Shanghai Syncores is based in Shanghai.

56. Shanghai Syncores developed the zinc chloride manufacturing process, at the lab scale. (Eric Gu 4/5/21 Dep. Tr., 60:6-10).

ZHP Defs.' Response: Admitted.

57. Shanghai Syncores and ZHP were required to conduct a genotoxic impurity analysis when they developed the zinc chloride process, and were aware of

the FDA guidance titled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" dated December 2008. (Eric Gu 4/5/21 Dep. Tr., 58:15-60:4).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that Dr. Gu testified that "[y]eah, based on our knowledge at the time, you know, if there was a suspected genotoxic impurity in the process, we will do the [genotoxic impurity] analysis." (Eric Gu 4/5/21 Dep. 60:1-4 (Pls.' SUMF Ex. 31).) They also admit that Dr. Gu testified he was familiar with the FDA guidance identified above. (*Id.* 69:8-10.) However, they deny Plaintiffs' assertion that they should have conducted such an analysis with regard to NDMA and NDEA or that the FDA guidance is relevant here. The FDA guidance document makes clear that it only applies "in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway." (*See* FDA, Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products (Dec. 2008) ("FDA Dec. 2008 Guidance for Industry") at 6 (Davidson Cert. Ex. 8).) Further, the document makes clear that it only "applies to known starting materials or anticipated reaction products," and that it "do[es] not establish legally enforceable responsibilities." (*Id.* at 1-2.) Thus, because the ZHP Defendants deny they knew or should have expected that NDMA or NDEA could form during the various processes, the FDA guidance statement is not implicated

and they were not required to perform a genotoxic impurity analysis for either substance.

58. In connection with the FDA Guidance titled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" dated December 2008, Mr. Gu confirmed that as a matter of risk assessment both ZHP and Syncores were responsible to know in 2011, as set forth in Section 4-A titled "Prevention of Genotoxic and Carcinogenic Impurity Formation," that, "Since drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing." (Eric Gu 4/5/21 Dep. Tr., 69:1-70:23).

ZHP Defs.' Response: Denied in Part. The ZHP Defendants admit that Dr. Gu confirmed that ZHP was responsible for knowing the statement set forth above in 2011. However, they deny Plaintiffs' assertion that this statement is relevant here. The FDA guidance document makes clear that it only applies "in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway." (*See* FDA Dec. 2008 Guidance for Industry at 6.) Further, the document makes clear that it only "applies to known starting materials or anticipated reaction products," and that

it "do[es] not establish legally enforceable responsibilities." (*Id.* at 1-2.) Thus, because the ZHP Defendants deny they knew or should have expected that NDMA or NDEA could form during the various processes, the FDA guidance statement is not implicated.

The ZHP Defendants also deny Plaintiffs' assertion that they did not conduct a full and proper appraisal of ZHP's process changes for valsartan API. Prior to adopting the Zinc Chloride process, ZHP conducted a detailed self-evaluation and assessment that included: "(1) Process changes content evaluation; (2) Suitability of specifications and analytical methods of intermediates and final substance evaluation; (3) Manufacturing equipment evaluation; (4) Assessment via lab-scale process research and development studies; (5) Quality risk assessment." (*See* ZHP02579954, at 962-65 (Davidson Cert. Ex. 9).) Similarly, as explained in an unexcluded portion of defense expert Dr. Ali Afnan's report, "[p]rior to submitting this Drug Master File amendment, ZHP ran a number of tests to determine the effect, if any, that adding the quenching would have on the [TEA] process. For example, in an internal summary of the valsartan process change, ZHP employees noted that '[a]dding sodium nitrite quenching operation can effectively remove azide ions in the reaction solution, and basically will not cause negative effects on product quality.'" (Amended Rep. of Dr. Ali Afnan, Ph.D. ("Afnan Rep.") ¶ 77, Jan. 11,

2023 (Davidson Cert. Ex. 10) (citing ZHP01838512 at 517 (certified translation at 4)).)

59. The 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" stated in part: "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." (Eric Gu 4/5/21 Dep. Tr., 65:3-65:24).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the May 1978 IARC Monograph contains the statement quoted above. However, that statement is irrelevant here because the ZHP Defendants did not know, nor should they have known, that dimethylamine would be present in the Zinc Chloride process for the reasons explained below. (*See infra* ¶¶ 60, 63.)

60. Mr. Gu could not identify anybody at Syncores who, "evaluated potential degradation of DMF as part of the zinc chloride process" during the development of the zinc chloride process. (Eric Gu 4/5/21 Dep. Tr., 77:21-78:10).

ZHP Defs.' Response: Admitted with clarification. While Mr. Gu testified that he did not "know who" evaluated the potential degradation of DMF solvent as part of the zinc chloride process, Mr. Gu never testified that no one evaluated the process. Moreover, the ZHP Defendants deny Plaintiffs' implicit assertion that Syncores should have evaluated the potential degradation of DMF solvent as part of the zinc chloride process. First, only a limited number of publications have even

suggested (in passing) that DMF solvent could decompose at its boiling point. (*See*, *e.g.*, Purification of Laboratory Chemicals, Armarego, WLF (4th Edition 1996, 6th Edition 2009) ("Armarego") ("DMF decomposes slightly at its normal [boiling point] (153C) to give small amounts of dimethylamine and CO").) Second, Plaintiffs' experts have conceded that the process never reached the temperature necessary for DMF to boil. (TPP Trial Defs.' SUMF Ex. 58, Najafi 2023 Dep. Vol. I 206:11-19; *see also id.*, Ex. 61, Deposition of Stephen S. Hecht, Ph.D. ("Hecht Dep.") 218:7-23, Jan. 13, 2023).)

The ZHP Defendants also deny Plaintiffs' assertion that they did not conduct a full and proper appraisal of ZHP's process changes for valsartan API. Prior to adopting the Zinc Chloride process, ZHP conducted a detailed self-evaluation and assessment that included: "(1) Process changes content evaluation; (2) Suitability of specifications and analytical methods of intermediates and final substance evaluation; (3) Manufacturing equipment evaluation; (4) Assessment via lab-scale process research and development studies; (5) Quality risk assessment." (*See* ZHP02579954, at 962-65.) Similarly, as explained in defense expert Dr. Ali Afnan's report, "[p]rior to submitting [the] Drug Master File amendment [for the TEA process], ZHP ran a number of tests to determine the effect, if any, that adding the quenching would have on the [TEA] process. For example, in an internal summary of the valsartan process change, ZHP employees noted that '[a]dding sodium nitrite

quenching operation can effectively remove azide ions in the reaction solution, and basically will not cause negative effects on product quality.'" (Afnan Rep. ¶ 77 (citing ZHP01838512 at 517 (certified translation at 4)).)

61. Mr. Gu confirmed that ZHP and Syncores were aware of the EMA guidelines titled "Guideline on the Limits of Genotoxic Impurities" in effect from January 1, 2007, to January 31, 2018 when developing the zinc chloride process and TEA process with sodium nitrite quenching. Section 4, titled "Toxicological Background," provided in part that "According to current regulatory practice, it is assumed that in vivo genotoxic compounds have the potential to damage DNA at any level of exposure and that such damage may lead/contribute to tumor development . . . Thus, for genotoxic carcinogens, it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk." Also, "some structural groups" including n-nitroso compounds including NDMA and NDEA, "were identified to be of such high potency that intakes even below the threshold of toxicological concern, or TTC, would be associated with a high probability of a significant carcinogenic risk...this group of high potency genotoxic carcinogens...have to be excluded from the TTC approach. Risk assessment of such groups requires compound-specific toxicity data." (Eric Gu 4/5/21 Dep. Tr., 90:6-97:16).

ZHP Defs.' Response: Denied. Mr. Gu actually testified that he can only "assume" that Syncores was aware of the referenced EMA guideline document and that he could only "suppose" ZHP knew of it, but he could not say "exactly if [ZHP] knew or not." (4/6/21 Gu Dep. 93:11-24; *see also id.* 95:11-21 (Mr. Gu would "assume" both companies were aware).) Moreover, "[i]f Plaintiffs [ ] were correct that any chemist should have known . . . that the TEA with quenching and Zinc Chloride processes were likely or even capable of causing nitrosamine formation, the expert chemists at the FDA would have been aware of these risks and flagged them in their valsartan ANDA reviews. There is no evidence anyone at the FDA had this concern prior to the identification of NDMA in valsartan in May 2018." (Afnan Rep. ¶ 145.) Thus, Plaintiffs have no factual support for the assertion that "ZHP was [ ] required to conduct a 'risk-based evaluation of the possible formation of nitrosamines resulting from their proposed process changes.'" (*Id.*)

62. ZHP "would have been aware these guidelines were put out in 2007 and ZHP would have known as of 2007 that nitrosamines, including NDEA and NDMA belonged to a class of very potent genotoxic carcinogens as of that time in 2007," which per the Guideline required control, "as low as reasonably practical," as opposed to according to the threshold of toxicological concern. (Eric Gu 4/6/21 Dep. Tr., 381:6-386:21 (Ex. 21)).

ZHP Defs.' Response: Denied. Mr. Gu did not testify in agreement with the quote. Counsel moved on before Mr. Gu expressed agreement or disagreement with his statement:

> Q. ZHP would have been aware these guidelines were put out in 2007 and ZHP would have known as of 2007 that nitrosamines, including NDEA and NDMA belonged to a class of very potent genotoxic carcinogens as of that time in 2007, correct?
>
> THE WITNESS: You said it.

(4/6/21 Eric Gu Dep. 386:12-21.)

Further, the EMA's Guideline on the Limits of Genotoxic Impurities only apply to those impurities "that might reasonably be expected based on knowledge of the chemical reactions and conditions involved." (*See* EMA, Guideline on the Limits of Genotoxic Impurities, at 4, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-limits-genotoxic-impurities_en.pdf (Davidson Cert. Ex. 11).) Thus, they are inapplicable here, because the ZHP defendants did not know about, or expect, the formation of NDMA and NDEA in valsartan. (*See generally* TPP Trial Defs.' SUMF ¶¶ 57-66.)

63. A 2009 article published in the scientific journal Tetrahedron Letters, titled: DMF, Much More Than a Solvent, indicated in part that "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of acidic or basic materials..." **Mr. Gu confirmed that it was known in the chemistry community**

that under certain circumstances DMF could decompose to yield dimethylamine. (Eric Gu 4/5/21 Dep. Tr., 172:13-174:9, 183:12-21).

ZHP Defs.' Response: Denied in part. The ZHP defendants admit that the 2009 article, which plaintiffs did not include as an exhibit, includes the quote set forth above. (*See* Muzart, N,N-*Dimethylformamide: much more than a solvent*, Tetrahedron 65 (2009) 8313–8323 (Davidson Cert. Ex. 12).) However, that article cites Armarego (*id.*), which in turn states only that DMF solvent "[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide" and that "[t]he decomposition is catalysed by acidic or basic materials, so that even at room temperature DMF is appreciably decomposed ***if allowed to stand for several hours with solid KOH, NaOH or CaH_2.***" (Armarego at 192 (emphasis added.) As Plaintiffs' experts have conceded, ZHP's process never reached the temperature necessary for DMF to boil. (TPP Trial Defs.' SUMF Ex. 58, Najafi 2023 Dep. Vol. I 206:11-19; *see also id.*, Ex. 61, Hecht Dep. 218:7-23), and only involved "acidic media." (TPP Trial Defs.' SUMF Ex. 58, Najafi 2023 Dep. Vol. I 211:13-17.) Thus, to the extent that Mr. Gu "confirmed that it was known under certain circumstances DMF could decompose to yield dimethylamine," the ZHP defendants deny those circumstances are relevant here.

64. Mr. Gu confirmed that the root cause for the formation of NDMA in the valsartan API manufactured with the zinc chloride process was in part

attributable to the degradation or decomposition of DMF to yield dimethylamine, and the reaction of nitrous acid with the dimethylamine. (Eric Gu 4/5/21 Dep. Tr., 178:24-181:4).

ZHP Defs.' Response: Admitted.

65. **Mr. Gu confirmed that Syncores did not evaluate the potential decomposition of DMF to yield DMA as part of the zinc chloride process**. (Eric Gu 4/5/21 Dep. Tr., 98:17-99:5).

ZHP Defs.' Response: Admitted with clarification. Mr. Gu explained in the testimony cited by plaintiffs that Syncores was unaware that DMF could decompose in the conditions present in the manufacturing processes at issue and, as a result, did not specifically test DMF solvent for DMA. The ZHP Defendants further deny that they knew or should have expected that DMF could degrade in the conditions present in the zinc chloride process. (*See supra* ¶¶ 60, 63, TPP Trial Defs.' SUMF ¶¶ 57-66.)

66. Qiangming Li, a 30(b)(6) witness, is the Senior Director of the Chuannan QC Department. (ZHP 255 (Ex. 121)).

ZHP Defs.' Response: Admitted.

67. Qiangming Li confirmed that ZHP received a series of customer complaints regarding unknown, or aberrant peaks on gas chromatography for

valsartan API, some of which were focused on the area surrounding toluene – where the NDMA peak was located. These included:

1. Ranbaxy/SunPharma on September 30, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 130:7-170:11 (Ex. 32); ZHP01748896, ZHP 260 (Ex. 33)).

2. Shanghai Pharmtech on November 20, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 177:22-199:20; ZHP01748905, ZHP 264 (Ex. 34)).

3. SunPharma on November 17, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 290:16-318:10 (Ex. 35); ZHP00405069, ZHP 277 (Ex. 36); ZHP01313866, ZHP 278 (Ex. 37)).

4. Vertex on December 21, 2016 (Qiangming Li 4/14/2021 Dep. Tr. 204:11-214:17; ZHP02630924, ZHP 265 (Ex. 38); ZHP02630926, ZHP 266 (Ex. 39).

5. Glenmark on December 29, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 254:22-290:4; ZHP00496153, ZHP 271 (Ex. 40); ZHP00496155, ZHP 272 (Ex. 41); ZHP02118712, ZHP 273 (Ex. 42)).

6. Aurobindo on August 23, 2017 (Qiangming Li 4/15/2021 Dep. Tr. 343:21-372:9; ZHP02094739, ZHP 281 (Ex. 43)).

7. Novartis on May 22, 2018 (Qiangming Li 4/15/2021 Dep. Tr. 386:17466:17; ZHP00405021, ZHP 284 (Ex. 44)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the documents identified above asked ZHP for information regarding certain unidentified peaks observed on gas chromatography for valsartan API and that some of those peaks occurred near the identified peak for toluene, where NDMA was eventually identified. However, the ZHP Defendants deny any suggestion that they inadequately responded to these requests for information. Indeed, Novartis

specifically thanked ZHP for its help and cooperation in connection with its request for information dated May 22, 2018, which is the request that led to the discovery of NMDA. (ZHP02113685, at 1 (Davidson Cert. Ex. 13).) Moreover, as the FDA itself noted, "NDMA's properties make it difficult to find," and "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it." (August 2018 Gottlieb Statement at 4.)

68. Qiangming Li testified that, "NDMA elutes near the toluene peak in the residual solvent gas chromatography of ZHP's valsartan API" and that ZHP never used GC-MS to test valsartan API prior to June 2018. (Qiangming Li 4/13/2021 Dep. Tr. 77:4-6 (Ex. 45); 4/14/2021 Dep. Tr. 168:11-17 (Ex. 32)).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that Mr. Li's deposition testimony included the quotes noted in Paragraph 68. However, the ZHP Defendants deny Plaintiffs' insinuation that they should have tested valsartan API with GC-MS. (*See* TPP Trial Defs.' SUMF ¶ 69.) At the time the VCDs at issue were approved by the FDA, and continuing through the time of the recalls beginning in July 2018, there were no validated or industry-standard methods or practices to test for the presence or absence of NDMA or NDEA in VCDs. (Afnan Rep. ¶ 182 ("GC-MS was not validated or shown to be suitable for the detection of NDMA/NDEA prior to May 2018."); *see also* FDA, Combined N-

Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay by GC/MS-Headspace, https://www.fda.gov/media/117843/download (FDA's Office of Testing and Research reporting that it "ha[d] developed a gas chromatography-mass spectrometry (GC/MS) headspace method to detect the presence of NDMA and NDEA in valsartan drug substances" in late August, 2018).)

68.5. Jie Wang is ZHP's Vice President of Corporate Business Development and VP of ZHP for marketing and sales of API and finished dose, and testified as a 30(b)(6) representative. Jie Wang confirmed that an internal ZHP email chain indicated that CEMAT was involved with the investigation of the "unknown peaks" including as of September 14, 2017 when an email indicated "CEMAT has details." (Jie Wang 5/18/21 Dep. Tr., 30:3-33:6, 35:10-37:16, 128:9-129:11 (Ex. 117)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that one of Mr. Wang's titles is correctly stated as "Vice President of Corporate Business Development," but Mr. Wang's curriculum vitae lists him as a Vice President for "Marketing & Business Development . . . on APIs & FDFs," not "marketing and sales of API and finished dose." (*See* Curriculum Vitae of Jie Wang at 1 (Davidson Cert. Ex. 14).) In addition, Plaintiffs have taken Mr. Wang's testimony regarding CEMAT out of context. Mr. Wang never "confirmed" that the cited email chain "indicated that CEMAT was involved with the investigation of the 'unknown peaks' as of September 14, 2017." Mr. Wang only testified that counsel read the statement

"CEMAT has details" regarding "Glenmark and Sun Pharma customers hav[ing] similar residual solvent complaints" as "basically the correct translation of the Chinese":

> Q. It says, "Glenmark and Sun Pharma customers have had similar residual solvent complaints before. CEMAT has details. The detailed investigation report, because it involves other residual solvents, it is not recommended to provide the report to Aurobindo at this time."
>
> A. Yes, I would say that that is basically the correct translation of the Chinese.

(5/18/21 Jie Wang Dep. 129:2-11 (Pls.' SUMF Ex. 117).)

69. Mr. Gu testified with regard to the "unknown peaks" that were seen on routine gas chromatography by ZHP and some of its customers. He confirmed that an unknown peak was required to be investigated by ZHP, but could not provide any specific reason why Novartis discovered that the unknown peak at issue indicated the presence of NDMA, before ZHP, stating that, "it was not so easy to detect" and "it's quite a challenging work." (Eric Gu 4/5/21 Dep. Tr., 210:24-219:5, 236:24--237:8).

ZHP Defs.' Response: Denied. Plaintiffs misrepresent Mr. Gu's testimony. Mr. Gu was not unable to "provide any specific reason why Novartis discovered" the unknown peak before ZHP. As Mr. Gu explained, there were several reasons that Novartis caught the peak before ZHP, including the fact that "each company do[es] their own studies" (4/5/21 Eric Gu Dep. 218:7-9) and that the levels of impurities

were very low and thus "not so easy to detect," meaning that companies had "to develop a specific method in order to discover, qualify, and quantify" them, which is "challenging work" (*id.* 218:19-219:5). And to the extent Mr. Gu could not answer counsel's specific questions about these issues, Mr. Gu explained that he was "not in the quality unit" and, therefore, did not know "what was happening" at the time. (4/5/21 Eric Gu Dep. 214:6-11; *see also, e.g.*, *id.* 215:7-22; 216:30-22.)

[Plaintiffs' SUMF omits Paragraph 70.]

71. When asked why, despite every batch showing the "NDMA peak just after the Toluene peak on the chromatograms. . . nobody at ZHP realized that it needed to be tested and identified," Mr. Gu stated that ZHP was aware of these peaks and, "did whatever they can," but ultimately that, **"They are struggling, I guess, in the past."** (Eric Gu 4/6/21 Dep. Tr., 333:21-335:19).

ZHP Defs.' Response: Denied in part. The referenced quotations from Mr. Gu's testimony are taken out of context. Mr. Gu never agreed that "every batch" showed the specific peaks that Plaintiffs' counsel claimed were present near the toluene peak. (*See* 4/6/21 Eric Gu Dep. 334:5-7.) To the contrary, Mr. Gu explicitly stated at his deposition that he does not "know the truth about, you know, how often [the peaks] appear in the final product" when counsel pressed Mr. Gu to agree with Plaintiffs' counsel's claim that the "peak was there on every single batch" that ZHP tested with GC-FID chromatography. (4/6/21 Eric Gu Dep. 339:13-340:22.)

Moreover, it was Plaintiffs' counsel—not Mr. Gu—who continually referred to unspecified peaks as the "NDMA peak." (*See, e.g.*, *id.* 333:23, 335:23, 338:18.) Dr. Gu stated that he was "sure ZHP look[ed] at . . . all those little peaks," and that they looked like "noise to him." (*Id.* 339:21-340:9.)

72. Mr. Gu confirmed that ZHP was obligated to update the valsartan API impurity profile with the FDA and European authorities at all times. (Eric Gu 4/6/21 Dep. Tr., 330:18-332:11).

ZHP Defs.' Response: Admitted.

73. The November 29, 2018 FDA Warning Letter found in part that ZHP, "failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. . . Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant, dimethylamine." Mr. Gu agreed that NDMA was a probable human carcinogen, but stated, "In 2011, okay, we didn't know. We didn't know that there were probable human carcinogens like NDMA or NDEA in the product." However, in this context, Mr. Gu agreed that, **"ZHP was responsible for the quality of the valsartan that it manufactured," and "Yes, you know, ZHP is responsible for the API they are making."** (Eric Gu 4/6/21 Dep. Tr., 360:8-374:12).

ZHP Defs.' Response: Denied in part. While the FDA warning later does include the referenced quotes, Mr. Gu explained—in response to Plaintiffs' counsel asking several times whether those statements were true and accurate—that the letter is "one person's observations," which are "not complete" and to which ZHP provided a response. (4/6/21 Eric Gu Dep. 364:7-366:7.) Also see response to Paragraph 47.

74. Mr. Gu also agreed with the statement in the FDA Warning Letter that if new or higher levels of impurities were detected, **ZHP was responsible to, "fully evaluate the impurities to take action to ensure the drug is safe for patient[s]."** (Eric Gu 4/6/21 Dep. Tr., 375:16-376:11).

ZHP Defs.' Response: Denied. Mr. Gu did not testify that he agreed with the statement, and Plaintiffs mischaracterize his testimony by cutting his answer off prematurely in their citation. What Mr. Gu actually testified is that "[he] [did not] know" if he could agree with the statement quoted above because "in the scientific process there is no such thing as fully" and "those are just vague statement[s]." (4/6/21 Eric Gu Dep. 376:12-377:5.) Also see response to Paragraph 47.

75. Peng Dong, a 30(b)(6) corporate representative, was the Deputy Director of the ZHP Technical Department, which was responsible, "to improve and upgrade the manufacturing process for the products under our management." (Peng Dong 3/29/21 Dep. Tr., 27:18-31:13).

ZHP Defs.' Response: Admitted.

76. Mr. Dong confirmed that the **ZHP internal protocol titled: Guideline for Genotoxic Impurity Evaluation** (No. API-R&D-002) (bates ZHP01447235-242 (Ex. 122)), Section 2, provided that, **"All intermediates and APIs produced under GMP conditions must be identified for genotoxic impurities," and per ICH the risk assessment evaluation included identification of genotoxic impurities and confirmation of the quality specifications of any API, including valsartan.** (Peng Dong 3/29/21 Dep. Tr., 33:9-34:10 (Ex. 46)).

ZHP Defs.' Response: Denied in part. Mr. Dong did not testify that "per ICH the risk assessment evaluation included identification of genotoxic impurities." Instead, the cited testimony is as follows:

> Q. Identification of genotoxic impurities is part of the risk assessment evaluation, correct?
> A. Per the requirements of ICH, we would confirm the quality specifications of API.

(3/29/21 Peng Dong Dep. 33:20-34:1 (Pls.' SUMF Ex. 46).)

77. Mr. Dong stated that in 2011 ZHP, "did not know whether DMF could decompose in the zinc chloride process for valsartan." The most he could say is that "Maybe an idea popped into someone's mind momentarily" or "it could be that suddenly someone dreamt about the scene." (Peng Dong 3/30/21 Dep. Tr., 161:8-17, 162:7-18, 163:15-23, 164:11-165:7, 166:13-167:6 (Ex. 47)).

ZHP Defs.' Response: Denied in part. While ZHP was not aware that DMF could decompose in the zinc chloride process for valsartan in 2011, the quoted portions of Mr. Dong's testimony were not "[t]he most he could say." As Mr. Dong explained, ZHP's "understanding about DMF [wa]s that DMF [wa]s a very stable solvent" which was "commonly used in the industry." (3/30/21 Peng Dong Dep. 161:18-3 (Pls.' SUMF Ex. 47); *see also id.* 162:19-163:14.) Further, Mr. Dong testified that none of the documents he reviewed indicated ZHP knew that it was possible that DMF solvent could degrade during the manufacturing process, and the information he reviewed indicated that ZHP did not have such knowledge. (*Id.* 166:13-167:6.)

78. ZHP's risk assessment was limited to evaluation of the newly added solvent DMF, "DMF was treated as a new impurity." ZHP could produce no documentation of any testing in 2011, "to find out whether DMF could...decompose or not during the zinc chloride process for valsartan." (Peng Dong 3/29/21 Dep. Tr., 167:7-168:19).

ZHP Defs.' Response: Denied in part. The ZHP defendants admit Mr. Dong testified that "DMF was treated as a new impurity." However, the second quote is taken out of context. Mr. Dong testified that:

> A. In 2011, ZHP had no understanding as to whether DMF could decompose during the zinc chloride process for valsartan.

> When it comes to the documents I have reviewed, I could not find any information regarding whether in 2011 testings were done to find out whether DMF could compose -- decompose or not during the zinc chloride process for valsartan.

Moreover, as explained above, there was no evidence at the time that DMF could degrade in the conditions present in the Zinc Chloride process. (*See supra* ¶ 63.)

The ZHP Defendants also deny Plaintiffs' assertion that ZHP's "risk assessment was limited to evaluation of the newly added solvent DMF." Prior to adopting the Zinc Chloride process, ZHP conducted a detailed self-evaluation and assessment that included: "(1) Process changes content evaluation; (2) Suitability of specifications and analytical methods of intermediates and final substance evaluation; (3) Manufacturing equipment evaluation; (4) Assessment via lab-scale process research and development studies; (5) Quality risk assessment." (ZHP02579954, at 962-65.)

79. The table of impurity evaluation at section 7.2.1.2 of the Change Request Form for the zinc chloride process actually confirms that, "Dimethylamine is not listed as a potential impurity that was evaluated." (Peng Dong 3/30/21 Dep. Tr., 213:10-22, 214:18-22, 215:19-216:19, 218:2-9).

ZHP Defs.' Response: Admitted.

80. Mr. Dong confirmed that, **"ZHP never assessed how nitrite or nitrous acid might react with dimethylamine as part of the zinc chloride process**

to manufacture valsartan between 2011 and June 2018." (Peng Dong 3/30/21 Dep. Tr., 227:1-7).

ZHP Defs.' Response: Admitted with clarification. While Mr. Dong did provide the testimony cited by Plaintiffs, his statement is taken out of context and inappropriately cut short. Mr. Dong explained that the reason ZHP did not perform this assessment was because "between 2011 to June 2018, the authorities, the industry, [and] ZHP did not have any understanding on the creation of nitrosamine impurities in valsartan products." (3/30/21 Peng Dong Dep. 227:1-10.) Further, as noted above, Mr. Dong explained that ZHP's "understanding about DMF [wa]s that DMF [wa]s a very stable solvent" which was "commonly used in the industry." (3/30/21 Peng Dong Dep. 161:18-3; *see also id.* 162:19-163:14.)

81. Mr. Dong discussed the zinc chloride process including the use of DMF as a reaction solvent "to dissolve raw materials during the reaction," and confirmed that **ZHP did not do any investigation into the potential for DMF to decompose and yield dimethylamine until June 2018."** (Peng Dong 3/31/21 Dep. Tr., 241:3-256:17 (Ex. 48)).

ZHP Defs.' Response: Denied. Mr. Dong testified that "ZHP conducted an investigation" in "June 2018, after NDMA was found," at which point "ZHP obtained" knowledge about NDMA formation. (3/31/21 Peng Dong Dep. 256:14-17 (Pls.' SUMF Ex. 48).) Mr. Dong never testified that ZHP did no investigation at all

into the potential for DMF to decompose and yield DMA. Further, it is unclear why Plaintiffs end their paragraph with a quotation mark since the emphasized language does not appear in the cited testimony.

82. Min Li confirmed the location on chromatograms of the peak attributable to the NDMA. (Min Li 4/20/21 Dep. Tr., 209:8-217:10).

ZHP Defs.' Response: Admitted with clarification. The specific testimony was related to Solvias' GC-MS chromatograms, which were not created until 2018. (*See* 4/20/21 Min Li Dep. 209:8-17.) With respect to ZHP's chromatograms, Dr. Li generally described where the NDMA peak was ultimately observed following its discovery in 2018. (4/20/21 Min Li Dep. 214:19-13.)

83. Dr. Li ultimately agreed that, **"the technology and the methodology was clearly available to identify the NDMA,"** as long as you "know what to look for" based on a risk assessment – which he confirmed is an ongoing process for the lifecycle of the drug. (Min Li 4/20/21 Dep. Tr., 230:9-19, 233:10-18).

ZHP Defs.' Response: Admitted with clarification. Dr. Li explained that there is an "ongoing" risk process, but that it was usually implemented "with a particular . . . reason." (4/20/21 Min Li Dep. 233:16-18.) However, because no one was aware of the potential for NDMA to form in valsartan, there was no reason to use the technology identified to test the API and it was neither the industry standard nor required by the FDA. Indeed, as Dr. Scott Gottlieb, the FDA Commissioner,

explained in a statement dated August 30, 2018: "Before [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process." (August 2018 Gottlieb Statement at 4.) Dr. Gottlieb also noted that "NDMA's properties make it difficult to find," and that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it." (*Id.*)

84. In the context of the November 28, 2018 FDA Warning Letter, Dr. Li confirmed that the FDA disagreed with ZHP's position that it could not have been expected to foresee or detect the NDMA due to a 'knowledge gap." With regard to the risk assessment, the FDA stated, **"You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change."** And the FDA stated further, "Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce." **Finally, the FDA**

confirmed, and Dr. Li agreed, that ZHP was "responsible for the quality of the drugs" produced by ZHP. (Min Li 4/21/21 Dep. Tr., 426:8-427:5, 430:11-434:10).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the quoted deposition testimony recites statements from the 2018 FDA Warning Letter, but none of the cited testimony indicates that "Dr. Li confirmed that the FDA disagreed with ZHP's position that it could not have been expected to foresee or detect the NDMA due to a 'knowledge gap.'" In the testimony immediately following the portions Plaintiffs cite, Dr. Li explains that the "FDA . . . basically acknowledged the knowledge gap . . . by both industry as well as regulators." (4/21/21 Min Li Dep. 431:19-432:1.) Indeed, the FDA itself noted in August 2018 that "NDMA's properties make it difficult to find," and that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it." (August 2018 Gottlieb Statement at 4.) In fact, the FDA went so far as to say that "[b]efore [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process." (*Id.*) Also see response to Paragraph 47.

85. Dr. Li confirmed that NDMA and NDEA were "drug-related impurities" as referenced in the FDA's 2008 Guidance for Industry, Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended

Approaches, which states that "drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, **every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing."** (Min Li 4/21/21 Dep. Tr., 296:23-298:4).

ZHP Defs.' Response: Admitted.

86. Dr. Li acknowledged that due to the "extremely high carcinogenic potency" of n-nitroso compounds including NDMA and NDEA the FDA's Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products excluded those substances from the threshold approach. The European Medicines Agency Guidelines on the Limits of Genotoxic Impurities in effect from 2007 to 2018 similarly stated that due to, "the potential to damage DNA at any level of exposure and that such damage may lead/contribute to tumour development....for genotoxic carcinogens [including NDMA and NDEA] it is prudent to assume that there is no discernible threshold and that any level of exposure carries a risk." (Min Li 4/21/21 Dep. Tr. 308:14-309:2, 322:2-323:13, 329:3-13, 339:5-340:6).

ZHP Defs.' Response: Denied in part. Dr. Li did not "acknowledge[]" the validity of the cited language from the EMA guideline, but simply agreed that he "underst[ood]" the quoted language from the FDA document and that plaintiffs' counsel had correctly read "that statement in that document." (*See* Min Li 4/21/21

Dep. 308:14-23, 329:3-13; *see also id.* 322:17-323:6 (Plaintiffs' counsel asking if Dr. Li "see[s]" the statement in the EMA guideline).) Moreover, the applicability of both documents turns on a recognition that there is a reasonable expectation that a genotoxic or carcinogenic substance may be created. As to the FDA guidance document, it only applies "in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway." (*See* FDA Dec. 2008 Guidance for Industry at 6.) Further, the document makes clear that it only "applies to known starting materials or anticipated reaction products," and that it "do[es] not establish legally enforceable responsibilities." (*Id.* at 1-2.) With respect to the cited EMA guideline, those guidelines only apply to impurities that "might reasonably be expected based on knowledge of the chemical reactions and conditions involved." (ZHP-206 at 4/8.) The ZHP Defendants did not know, and did not have reason to expect, that NDMA or NDEA could form during the various processes.

87. Dr. Li also discussed the ICH guideline titled, "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7," dated February 6, 2013. This regulatory guideline stated that **cohort of concern carcinogens**, which, "may occur as impurities in pharmaceuticals," **are to be excepted from the Threshold of Toxicological Concern approach, because they, "display extremely high carcinogenic**

potency. Acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline." **Dr. Li confirmed that per the ICH guideline the threshold approach would not apply to these substances.** (Min Li 4/21/21 Dep. Tr. 381:1-390:20, 467:14-470:7).

ZHP Defs.' Response: Denied in part. While the cited ICH-M7 guideline was addressed at Dr. Li's deposition, Plaintiffs misinterpret the testimony on this issue. A plain reading of the scope of the guidelines makes clear that ICH M7 only applies to "new drug substances and new drug products during their clinical development and subsequent applications for marketing" and "new marketing applications and post approval submissions for marketed products," and those guidelines were "not intended to be applied retrospectively." (ZHP-310 at 1, 3.) Dr. Li similarly explained that "the degradants that we discuss here or the document discuss[ed] here is typically related to after the making of a drug substance" and that degradation that may occur during the API manufacturing process is "outside the scope" of M7. (4/21/21 Min Li Dep. 386:13-387:17.) Because ICH M7 only became effective in May 2015, after the process changes at issue, it is irrelevant to ZHP's risk assessment process here. (*See* M7(R1), at 1 & n.1, https://www.fda.gov/media/85885/download.) And, in any event, the ZHP Defendants did not know or expect that NDMA or NDEA could form during the valsartan API manufacturing processes. (*See, e.g.*, August 2018 Gottlieb Statement.)

88. Dr. Li acknowledged a textbook, Purification of Laboratory Chemicals, published in 1996 through 2000, which reflected "scientific knowledge as of the late 1990s and 2000" that DMF could decompose to yield dimethylamine. (Min Li 4/21/21 Dep. Tr. 391:13-395:5).

ZHP Defs.' Response: Denied. Dr. Li never agreed that the textbook "reflected" scientific knowledge in the late 1990s and 2000; he only agreed that counsel had correctly read a sentence contained within the textbook:

> Q. This textbook documents scientific knowledge as of the late 1990s and 2000 that DMF decomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide. ***That's what's stated in that first sentence, correct?***
>
> A. Mm-hmm.
>
> . . .
>
> Q. That's what that sentence says, correct?
>
> A. That's what sentence says, yes.

(4/21/21 Min Li Dep. 394:3-395:5 (objections omitted) (emphasis added).) Moreover, the ZHP Defendants deny that the textbook could have put ZHP on notice that DMF solvent could or would decompose to yield dimethylamine in the conditions present in the Zinc Chloride process even if ZHP had known about the book. (*See supra* ¶¶ 60, 63.)

89. Dr. Li acknowledged another scientific article published in 2009 titled "N.N-Dimethylformamide: much more than a solvent," which also recognized that

DMF could decompose to produce dimethylamine, referencing a textbook published in 1966. (Min Li 4/21/21 Dep. Tr. 411:19-413:22).

ZHP Defs.' Response: Denied in part. Plaintiffs' reference to "a textbook published in 1966" is misleading, given that the cited textbook is Purification of Laboratory Chemicals—i.e., a prior version of the same textbook cited in Paragraph 88, not a different source. (*See* 4/21/21 Min Li Dep. 412:15-413:15.) Moreover, the ZHP Defendants deny that the textbook or the referenced 2009 "scientific article" could have put them on notice that DMF could decompose to yield dimethylamine in the conditions present in the Zinc Chloride process even if they had known about them. (*See supra* ¶¶ 60, 63.)

90. Dr. Li acknowledged an article authored by a group from Beijing University of Technology published in 2010 in the Journal of Physical Chemistry titled "Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Triethylamine," which included a discussion of the formation mechanism of NDMA from the reaction of dimethylamine and nitrous acid – exactly what occurred here with the zinc chloride process. (Min Li 4/21/21 Dep. Tr. 414:2-416:12).

ZHP Defs.' Response: Denied in part. As an initial matter, Plaintiffs have misstated the title of the article, which is "Theoretical investigation of N-nitrosodimethylamine formation from nitrosation of trimethylamine." (*See* Sun et

al., *Theoretical Investigation of* N-*Nitrosodimethylamine Formation from Nitrosation of Trimethylamine*, J. Phys. Chem. A 2010, 114, 455-465 (Davidson Cert. Ex. 15).) This is important, because "trimethylamine" was never used in either the TEA with quenching process or the Zinc Chloride process. Moreover, while the ZHP Defendants admit that it was known that dimethylamine and nitrous acid could react to form NDMA, they deny that they knew or had reason to expect that dimethylamine was present in the Zinc Chloride process. (*See supra* ¶¶ 60, 63.) As Dr. Li went on to explain, while "retrospectively" the findings of this article may seem relevant, "the minor decomposition of DMF . . . was just not" in the "knowledge base." (4/21/21 Min Li Dep. 418:21-419:3.)

91. Due to a "knowledge gap" nobody at ZHP "considered the potential decomposition of the DMF to yield dimethylamine as part of the process." This included **no indication that anybody at ZHP reviewed scientific literature on the subject, despite the requirement by the ICH guideline to do so.** (Min Li 4/21/21 Dep. Tr. 408:13-24, 409:16-410:21).

ZHP Defs.' Response: Denied. Dr. Li did not testify that there was "no indication" that anyone at ZHP had reviewed any scientific literature on the potential decomposition of DMF. Dr. Li testified that he could not answer that question because he "was not there" and he had not "seen" any such indication. (4/21/21 Min Li Dep. 409:16-410:10.) Further, Dr. Li testified that "in general during the . . .

process development, ZHP's . . . process chemists look[ed] at the . . . degradation issues," but the "knowledge gap" kept them from this "particular issue" (4/21/21 Min Li Dep. 406:21-407:21), and noted that Plaintiffs' counsel's assertion that DMF decomposition "wasn't researched at all" was "speculation" (4/21/21 Min Li Dep. 409:1-14). Moreover, the ZHP Defendants deny that the information available at the relevant time demonstrated that DMF solvent could or would degrade in the conditions present in the Zinc Chloride process. (*See supra* ¶¶ 60, 63.)

92. ZHP's deviation investigation report listed Shandong Hualu Hengsheng Chemicals as a supplier of ZHP's DMF for use in the zinc chloride process. (PRINSTONO0075959-60 (Ex. 10)). **The certificate of analysis from that supplier documented dimethylamine as an impurity in the DMF as purchased.** (Shandong Hualu-Hengsheng Chem Co., *Certification of Analysis for N,H-Dimethylformamide* (Ex. 49)). Importantly, the certificate of analysis is for batch number "20101026," indicating that the batch was produced in 2010. The same deviation investigation report lists Zhejiang Jianye Chemicals Co. Ltd. as a supplier of ZHP's triethylamine, the namesake of the TEA process. (PRINSTONO0075957). That company's certificate of analysis for triethylamine, dated November 12, 2012, and also available online, lists DEA as an impurity in the solvent as purchased. (Ex. 50).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit the first sentence of Paragraph 92. However, Plaintiffs have not cited any evidence or testimony connecting the cited certificate of analysis to the at-issue VCDs, or any evidence that the cited certificate of analysis applied to the DMF solvent purchased and used in ZHP's manufacturing processes. Further, the certificate of analysis does not identify dimethylamine as an impurity in DMF solution but instead identifies the "alkalinity" of the substance and uses the molecular weight of dimethylamine to calculate alkalinity. In fact, Plaintiffs' unsupported statement that the batch number "indicat[es] that the batch was produced in 2010" flies in the face of Plaintiffs' counsel's admission that Plaintiffs "don't know the date of the document." (Dep. of Fengtian Xue, Ph.D. 146:6-18, Feb. 3, 2023 (Davidson Cert. Ex. 16).) Further, while Zhejiang Jianye Chemicals Co. Ltd. was a supplier of triethylamine to ZHP, it was ***not*** a supplier of triethylamine hydrochloride, which is the material that was used in the TEA process to manufacture valsartan, as highlighted by the same document Plaintiffs cite. (*See* TEA DIR at 148 of 236 (listing the "four suppliers of triethylamine hydrochloride raw materials in Huahai since 2010," which does not include Zhejiang Jianye Chemicals Co. Ltd.).)

93. Dr. Li confirmed that the solvents contained the secondary amine impurities that were needed to form NDMA and NDEA, as purchased: **"in some of the TEA raw material it may contain a trace amount of, you know, of**

dimethylamine, okay, so that's one root cause..." (Min Li 4/20/21 Dep. Tr. 77:8-80:16).

ZHP Defs.' Response: Denied in part. In the cited testimony, Dr. Li only states that he "***think[s]***" that the TEA raw materials "***may***" contain trace amounts of DMA. (*See* 4/21/21 Min Li Dep. 78:17-79:1.) He did not "confirm[]" that was definitively the case.

94. The TEA DIR also documented ZHP's understanding that dimethylamine was a known impurity of the raw DMF used in the zinc chloride process: "NDMA is generated by nitrosation reaction of the simultaneously presented dimethylformamide **(containing degradation product/impurity dimethylamine)** and nitrous acid; NDEA is similar to NDMA in structure, and the formation mechanism is similar too, i.e., Nitrosation of diethylamine." (TEA DIR at 145 of 236).

ZHP Defs.' Response: Admitted with clarification. The "TEA DIR" only "document[s] ZHP's understanding" as of November 5, 2018—i.e., the date of the DIR, which came after ZHP's investigation following the recall of valsartan. (*See* TEA DIR at -797.)

95. ZHP further confirmed that it was understood that DMF would include dimethylamine as an impurity – since it was confirmed that introduction of the DMF was enough to ensure the NDMA would be formed, in the ZHP Deviation

Investigation Report dated July 20, 2018 (DC-18001, ZHP00004363-4471 (Ex. 14)) ("ZNCL DIR"), as also discussed in the TEA DIR cited above. On page 19 of 33, ZHP stated, "Based on the above elucidated root cause, the presence of trace amount of NDMA in the final valsartan API requires the convergence of the following three factors: i) use of **dimethylformamide (DMF)** in the tetrazole formation step, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product." These are the same three factors described in the TEA DIR. This is further reiterated on page 22 of 33, including, "It seems clear that NDMA is only formed in Process II (ZNCL) associated with the use of solvent dimethylformamide (DMF) during the quenching of unreacted azide AND in the presence of the product of that step, indicating NDMA is a process impurity in Process II (ZNCL)."

ZHP Defs.' Response: Admitted with clarification**.** Both documents only reflect ZHP's knowledge as of 2018, after the impurities were discovered and after ZHP conducted its investigation following the recall. (*See* ZHP00004352 at -363 (dated July 20, 2018) (Pls.' SUMF Ex. 14); TEA DIR at -797 (dated November 5, 2018).) Thus, neither document speaks to ZHP's knowledge during the events at issue in this case, and they do not suggest that "it was understood that DMF would include dimethylamine as an impurity" at the time the Zinc Chloride process was being used to manufacture valsartan API. Plaintiffs have not provided any evidence that ZHP knew or should have expected that the triethylamine hydrochloride used in

manufacturing valsartan API may have been contaminated with DEA or that the DMF solution it used may have been contaminated with DMA.

95.5. ZHP never investigated the potential for NDMA or NDEA formation in the TEA with sodium nitrite quenching process or for the chemical interactions of triethylamine, diethylamine, dimethylamine, and sodium nitrite in that process before preparing its ZNCL DIR and TEA DIR. (ZHP00004371-72 (Ex. 14); PRINSTONO0075804-05 (Ex. 10)). In fact, it was the EDQM that brought the idea of potential NDEA contamination to ZHP's attention in the first place in August 2018. (PRINSTONO0075804-05).

ZHP Defs.' Response: Admitted with clarification. The ZHP Defendants admit that, prior to 2018, they had not "investigated the potential for NDMA or NDEA formation in the TEA with sodium nitrite quenching process or for the chemical interactions of triethylamine, diethylamine, dimethylamine, and sodium nitrite in that process" because the ZHP Defendants had no reason to suspect the reactions that led to the formation of NDMA and NDEA. The ZHP Defendants deny that they knew or should have expected that NDEA or NDMA could form during the process such that they should have investigated the potential for NDEA or NDMA to form. (*See generally* TPP Trial Defs.' SUMF ¶¶ 57-66.) The ZHP Defendants admit that "during [a] teleconference with EDQM and other EU authorities on August 07, 2018, Huahai was asked if there was the possibility that

N-Nitrosodiethylamin (NDEA) could be formed during the TEA valsartan process." (TEA DIR at 2 of 236.)

96. The May 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, discussion on N-nitroso compounds, indicated that, "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA.**" Dr. Li confirmed that this reaction is what occurred in the zinc chloride process: "the zinc chloride process for the formation of NDMA, you know, was also under the acidic, you know, pH. So, yes, so from that perspective, yeah, they are consistent." He also confirmed that this is information "scientists would be aware of and have available to them" in 2011.** (Min Li 4/21/21 Dep. Tr. 458:13-465:11).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that the May 1978 IARC Monograph contains the statement quoted above, but the ZHP Defendants deny that they knew or should have expected that dimethylamine would be present in the Zinc Chloride process for the reasons previously explained. (*See supra* ¶¶ 60, 63.) Further, Dr. Li did not "confirm[] that this reaction is what occurred in the zinc chloride process." Dr. Li stated that "the zinc chloride process for the formation of NDMA . . . was also under . . . acidic . . . pH" and that this is "consistent" with what is in the monograph. (4/21/21 Min Li Dep. 460:16-461:4.)

97. Dr Li acknowledged that it was known, as stated in the 1978 Monograph that, "The principal techniques employed for the analysis of volatile N-nitrosamines [including NDMA] have been described in a recent publication... high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is particularly important." (Min Li 4/21/21 Dep. Tr. 458:13-465:11).

ZHP Defs.' Response: Denied. Dr. Li did not "acknowledge[]" that the quoted language "was known." In fact, Dr. Li disputed counsel's assertion that it was known, explaining that the "description itself is very vague" and "without knowing . . . the detail [of] what this particular . . . sentence is referring [to] . . . it's very difficult . . . to assess." (4/21/21 Min Li Dep. 463:7-464:9.) When counsel repeated the question, Dr. Li again confirmed that the words appeared on the page—not that he agreed with counsel's statement:

> Q. You would agree with me that at least as of 1978 when this IARC monograph was published, it was known that mass spectrometry was an important confirmatory technique to identify nitrosamines such as NDMA, correct?
>
> . . .
>
> A. Here ***it just said***, yeah, the principal technique, yeah, for the analysis of volatile N-nitrosamine.

(4/21/21 Min Li Dep. 464:10-20.) Further, the head of the FDA, Dr. Scott Gottlieb, noted in an August 2018 statement that "NDMA's properties make it difficult to

find," and that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it." (August 2018 Gottlieb Statement at 4.)

98. Dr. Li acknowledged that a draft of the ZHP Deviation Investigation Report titled "Investigation Regarding an Unknown Impurity (Genotoxic Impurity)," indicated, **"Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation products were studied, and was unaware of the further reaction between degradation products and raw material."** (Min Li 4/22/21 Dep. Tr. 528:5-531:4 (Ex. 51)).

ZHP Defs.' Response: Admitted with clarification. This document was only a draft document, and Plaintiffs have not identified a final, approved and signed version of the document that contains the statement. At Dr. Li's deposition, Plaintiffs' counsel refused to provide Dr. Li with the final version of the document despite his request for one, and Dr. Li accordingly tried to clarify that the statement was a conclusion reached "as of the time this document was drafted." (4/22/21 Min Li Dep. 529:1-531:4 (Pls.' SUMF Ex. 51).) Further, the draft document goes on to explain that "[w]ith the development and progress of science, as well as the in-depth understanding and research on the potential genotoxic impurities, this issue is gradually resolved." (ZHP00662283 at -308 (Davidson Cert. Ex. 17).) Further, the

ZHP Defendants note that "[b]efore [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during [the Zinc Chloride] process." (August 2018 Gottlieb Statement at 4.)

99. Jucai Ge, ZHP's Quality Assurance Director, API Division and a 30(b)(6) corporate representative, was one of the recipients of the July 27, 2017 email from Dr. Lin. She confirmed that the technology to identify NDMA was available prior to June 2018, **"Had we known prior to June 2018 that there was an impurity called NDMA, I believe my company would have been capable of developing such an analytical method for this impurity, just like what we did when we became aware of such an impurity in June 2018.** (Jucai Ge 5/26/22 Dep. Tr., 119:7-120:21).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that Ms. Ge was a recipient of the July 27, 2017 email and that her testimony is accurately quoted. However, Ms. Ge did not state that the technology to identify NDMA in valsartan API was "available" prior to June 2018, but instead noted that ZHP was "capable of developing" the method. The ZHP Defendants deny that they, the industry or regulators had a reason to develop a method to test for the presence of NDMA or NDEA in valsartan until after the discovery of these impurities in 2018.

100. Jun Du testified with regard to the quality agreement between ZHP and Prinston that was applicable to the sales of valsartan, and confirmed that "The finished dose facility of ZHP was supposed to make sure that their API would comply with the requirements of the GMP." (Jun Du 5/27/21 Dep. Tr. 90:6-21).

ZHP Defs.' Response: Admitted.

101. Prinston did not ever test the finished dose based on its position that this was the responsibility of ZHP as the finished dose manufacturer per the terms of the quality agreement, according to Hai Wang. (Hai Wang 3/10/21 Dep. Tr. 152:8-153:16).

ZHP Defs.' Response: Denied in part. Mr. Wang testified "[t]he answer is no" when Plaintiffs' counsel asked him "did Prinston or Solco or Huahai US ever independently attempt to confirm the contamination levels with the NDMA impurity of the finished dose products sold to you by ZHP." (Hai Wang 3/10/21 Dep. 152:8-15.) Further, after responding "the answer is no," Mr. Wang continued that, "[i]t's a manufacturer's responsibility," referring to the responsibility to test to confirm contamination levels, as is "clearly spelled out in the quality agreement, because neither Prinston nor Solco manufactured the [finished dose] product in concern." (*Id.* 152:15-19.)

102. Hai Wang testified that the manufacturing process utilized by ZHP to manufacture the valsartan was of no interest to Prinston and Solco. (Hai Wang 3/10/21 Dep. Tr. 166:9-170:11).

ZHP Defs.' Response: Denied in part. As an initial matter, Mr. Wang testified on behalf of Solco, not Prinston. Further, Mr. Wang merely testified in his personal capacity as the "president of the marketing and sales for the finished product" that he was "not aware" of anyone referring to the API manufacturing process as the "zinc chloride process" because he had "nothing to do with that" (3/10/21 Hai Wang Dep. 166:9-167:22), and when asked if Solco was "supposed to know how the product is manufactured," he explained that the question was "way too vague" since "[e]ach personnel had its own responsibilities" and, "for marketing purposes," they did not need that particular type of knowledge (*id.* 168:3-14).

103. Minli Zhang, was the head of QA for Xunqiao, and was responsible for quality testing and in-process research. (Minli Zhang 3/22/2021 Dep. Tr. 41:23–43:9 (Exs. 52-53)).

ZHP Defs.' Response: Admitted with clarification. Ms. Zhang testified that she was "responsible for quality testing and ANDA research," and "the work that [she] had to do was in-process research, investigating and verification for the products in the context of the ANDA." (3/22/21 Minli Zhang Dep. 42:20-24 (Pls.' SUMF Ex. 53).)

104. The Chuannan and Xunqiao sites were about an hour away from one another by car. (Minli Zhang 3/22/2021 Dep. Tr. 35:18–23).

ZHP Defs.' Response: Admitted.

105. Chuannan, where the API was manufactured, was treated like a supplier. (Minli Zhang 3/22/2021 Dep. Tr. 99:14–23).

ZHP Defs.' Response: Admitted with clarification. Ms. Zhang testified that Xunqiao viewed Chuannan as a supplier in certain contexts. (3/22/21 Minli Zhang Dep. 99:14-100:13.)

106. Xunqiao, where the finished dose was manufactured using the contaminated API manufactured in Chuannan, never conducted its own residual solvent testing of the valsartan API manufactured at Chuannan, and instead relied on the reported testing conducted at Chuannan. (Minli Zhang 3/24/2021 Dep. Tr. 316:12–317:24 (Ex. 54)).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that Ms. Zhang testified: "If we're speaking of the API used in the commercialization batches, indeed, we didn't conduct residual solvent tests on the API." (Minli Zhang 3/24/2021 Dep. 317:21-24 (Pls.' SUMF Ex. 54).) The ZHP Defendants otherwise deny this paragraph as an incorrect characterization of Ms. Zhang's testimony. As an initial matter, both Chuannan and Xunqiao are ZHP manufacturing sites and that residual solvent testing was conducted at Chuannan, as Plaintiffs acknowledge

above, before the API was sent to the Xunqiao site to be incorporated into finished doses. (*See supra* ¶ 105.) Moreover, contrary to Plaintiffs' assertion that "Xunqiao . . . never conducted its own residual solvent testing of the valsartan API manufactured at Chuannan," Ms. Zhang testified that she believed "Xunqiao conducted residual solvent testing of valsartan API manufactured at Chuannan in conjunction with the manufacturing of the submission batches." (Minli Zhang 3/24/2021 Dep. 317:21-24.)

107. Remonda Gergis, Prinston's Vice President of Quality Assurance (ZHP 88), confirmed that Prinston expected ZHP to follow the specifications they set forth for their finished drug products, before selling the finished dose pills in the United States. (Remonda Gergis 2/1/2021 Dep. Tr. 115:13–116:6 (Ex. 55)).

ZHP Defs.' Response: Admitted with clarification.[5] In response to Plaintiffs' counsel's question about why it was important for Prinston to "develop their own official compilation of specifications used to ensure the strength, quantity, and purity of finished dose and API," Ms. Gergis testified as follows:

"THE WITNESS: Prinston is responsible for their ANDAs, so, therefore, we -- we have to put the specifications that was approved by the FDA in certain formats.

[5] It appears that Plaintiffs inadvertently failed to attach deposition exhibit "ZHP-88" as an exhibit to their SUMF.

And that is -- [those specifications] represent our expectation from Huahai, from ZHP, to follow and to -- to get their results -- or compare their results against."

108. ZHP has stipulated to the material gaps in its risk assessment of the zinc chloride process:

> Pursuant to Special Master Report and Order No. 56, in exchange for Plaintiffs' agreement not to further examine a witness at deposition regarding the statements identified herein, Defendant Zhejiang Huahai Pharmaceutical Co., Ltd. ("ZHP") hereby stipulates as follows:
>
> 1. ZHP states that there are no health benefits associated with the presence of NDMA or NDEA in valsartan.
>
> 2. ZHP states that the publication *Purification of Laboratory Chemicals* (4th ed.) by W.L.F. Armarego and D.D. Perrin, which was first published in 1996 and documented scientific knowledge at that time, states on page 192 that DMF "[d]ecomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide."
>
> 3. ZHP states that it was required to perform a risk assessment in connection with the process change to the zinc chloride process. ZHP further states the following:
>
> a) ZHP states that the scientific research relied on to use DMF as part of the zinc chloride process did not include scientific research into the potential decomposition products of DMF under the conditions of the zinc chloride process.
>
> b) The risk assessment of DMF did not specifically evaluate whether DMF was degrading to yield dimethylamine as part of the zinc chloride process.
>
> c) Therefore, there is no document from Shanghai SynCores or ZHP that documents that potential degradation of DMF as part of the zinc chloride process was evaluated as part of the risk assessment for the zinc chloride process.

d) ZHP states that it did not perform a risk assessment on the potential degradation of DMF because it did not realize that DMF would degrade in the way it ultimately degraded in the zinc chloride manufacturing process of valsartan. ZHP is not saying that it was not possible to know that DMF could degrade.

e) ZHP never identified the nitrosamine impurities in connection with its 2011 Risk Assessment and therefore did not evaluate the nitrosamine impurities as part of any steps of the risk assessment process.

4. With regard to the Change Request Form identified as Exhibit 195 to the March 28/29, 2021 deposition of Peng Dong (copy of Exhibit attached hereto as Exhibit 1), ZHP states the following:

a) The "Explanation Section" in Section 2 of the Change Request form on the page bearing Bates number ZHP01843067 provides a summary of the explanation for why the process change from the triethylamine hydrochloride process to the zinc chloride process was undertaken.

b) One of the reasons for the quality review described in Section 3 of the Change Request Form on the page bearing Bates number ZHP01843069 was to identify impurities due to the new process.

c) Section 3 of the Change Request Form on the page bearing Bates number ZHP01843070 provided that if this change was against CGMP code, it was supposed to be rejected.

(Ex. 91).

ZHP Defs.' Response: Denied in part. The ZHP Defendants admit that they stipulated to the statements included in Exhibit 91 that are reproduced in this paragraph. However, they deny Plaintiffs' mischaracterization of those stipulations as the ZHP Defendants having "stipulated to the material gaps in [ZHP's] risk assessment of the zinc chloride process."

ZHP cGMP Expert David Chesney

109. ZHP's class certification CGMP expert David Chesney agreed that the November 2018 FDA Warning Letter to ZHP, "summarizes significant deviations from current good manufacturing practices (CGMP) for active pharmaceutical ingredients (API)." (David Chesney Dep. Tr. 320:24-321:6 (Ex. 56)).

ZHP Defs.' Response: Denied. Mr. Chesney did not agree that the FDA letter summarized significant cGMP deviations. Instead, Plaintiffs asked Mr. Chesney whether the referenced quote appeared in the 2018 FDA Warning Letter, and Mr. Chesney confirmed that it did:

> Q. And right there on the first page in the second sentence ***it says***, "This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API)," right?
>
> A. Yes.

(Chesney Dep. 320:24-321:6 (emphasis added) (Pls.' SUMF Ex. 56).) Mr. Chesney did not testify that he agreed with that statement, and, as Mr. Chesney explained in his deposition, the Warning Letter Plaintiffs quote "makes certain assertions, but it's not the complete story." (*Id.* 333:12-14.) Also see response to Paragraph 47.

110. Mr. Chesney confirmed, "[t]he failure to adequately assess the potential formation of mutagenic impurities when ZHP implemented the new process, that would be a CGMP violation." (David Chesney Dep. Tr. 329:9-331:16).

ZHP Defs.' Response: Admitted with clarification. In the cited testimony, Mr. Chesney agreed that "[t]he failure to adequately assess the potential formation of mutagenic impurities when ZHP implemented the new process," it if had occurred, "would be a CGMP violation." He did not state that ZHP failed to adequately assess the potential formation of mutagenic impurities.

111. Mr. Chesney confirmed another CGMP violation. As stated by the FDA in the Warning Letter, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change." (David Chesney Dep. Tr. 331:17-332:5).

ZHP Defs.' Response: Denied. While Mr. Chesney did confirm that the foregoing quote from the 2018 Warning Letter was read correctly, Mr. Chesney did not confirm that any cGMP violation occurred in this case. As Mr. Chesney explained in his deposition, the Warning Letter Plaintiffs quote "makes certain assertions, but it's not the complete story." (Chesney Dep. 333:12-14.) Also see response to Paragraph 47.

112. Mr. Chesney agreed with the FDA's description of ZHP's duties: "You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher

levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." (David Chesney Dep. Tr., at 332:721).

ZHP Defs.' Response: Admitted.

113. Mr. Chesney agreed with the FDA, "that common industry practice may not always be consistent with CGMP requirements and that you [the manufacturer] are responsible for the quality of drugs you produce." (David Chesney Dep. Tr., at 335:12-336:2).

ZHP Defs.' Response: Admitted.

114. Mr. Chesney acknowledged the FDA's concern over ZHP's failure to adequately assess, "ghost peaks," and the "[f]ailure of [ZHP's] quality unit to ensure that quality-related complaints are investigated and resolved." (*Id.* at 321:21-322:4). As stated by the FDA, "Our investigation also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms." (*Id.* at 326:2-7). The FDA stated:

> ..."Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was expected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further."

* * *

> ..."FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation."

(*Id.* at 326:8-328:3). Mr. Chesney agreed that, "if you identify either the potential or the actual occurrence of [a genotoxic] impurity, then certainly it's important to understand it." (David Chesney Dep. Tr. 134:22-135:15).

ZHP Defs.' Response: Denied in part. While Plaintiffs accurately quote the FDA's 2018 Warning Letter, and Mr. Chesney did testify it was important to understand the potential or actual occurrence of a genotoxic impurity, Mr. Chesney did not "acknowledge[] the FDA's concern over ZHP's failure to adequately assess, [sic] 'ghost peaks,' and the '[f]ailure of [ZHP's] quality unit to ensure that quality-related complaints are investigated and resolved.'" (Pls.' SUMF ¶ 114.) Indeed, the quoted portion of Mr. Chesney's deposition does not include the words "ghost peaks," or refer to the FDA's use of that term. Further, Mr. Chesney merely testified that portions of the 2018 Warning Letter that were read to him were accurately quoted, not that he substantively agreed with the statements made therein:

> Q. Let's go through number 1 a little bit. "Failure of your quality unit to ensure that quality-related complaints are investigated and resolved." It says, "valsartan API." ***You've read*** this paragraph, right?

> A. I have. And I've also read ZHP's response to all this to get some balance to the situation.

(Chesney Dep. 321:21-322:6 (emphasis added).)

Also see response to Paragraph 47.

115. Mr. Chesney agreed that if one were to assume that there was not an available analytical method to test for and establish that the unknown peaks on the gas chromatography were due to NDMA (or NDEA) or another genotoxic impurity in the valsartan prior to June 2018 (despite ZHP's witnesses' agreement that the analytical methods existed), then one could not sell the drug product while knowing that there was the **potential** for an unknown unreasonably dangerous impurity: "**You should not go forward unless there's a persuasive reason to believe that the formation of these impurities would be at such a low level that it would not present a risk to human health**." (David Chesney Dep. Tr. 167:2-21).

ZHP Defs.' Response: Denied. Plaintiffs mischaracterize the hypothetical posed to Mr. Chesney and his response. As Mr. Chesney explained immediately prior to the portion of his testimony cited by Plaintiffs, there is a difference between a "potential" and a "real" or "significant" risk:

> A. Again, I would agree ***if and only if*** the weight of the science argued that there was a ***significant risk*** of formation of NDMA. There are literature references which you've shown me that showed in a laboratory setting people that identified this as a ***potential risk*** that's of concern, they should consider that.

> But it would take a more wholistic assessment to understand whether that was a ***real risk***, and decide accordingly whether to proceed with that process change at that time.

(Chesney Dep. 166:4-16 (emphasis added).)

Plaintiffs then reframed their hypothetical, asking Mr. Chesney to assume: (1) "a reasonable scientific expert in this field would say, Yes, this would be considered a ***real risk*** that this manufacturing process could create NDMA or other genotoxic impurities"; and that (2) "no test existed that could have measured whether or not this genotoxic impurity was actually being created," and Mr. Chesney agreed that the process change should not go forward under those circumstances. (Chesney Dep. 167:2-21 (emphasis added).) But Mr. Chesney did not state or suggest that was the case.

116. Mr. Chesney confirmed that the responsibility for quality deficiencies is an executive responsibility, "the leaders of the company, right up to the highest executive, would have the ultimate responsibility for this quality problem," (David Chesney Dep. Tr., 229:22-230:1, 230:9-16).

ZHP Defs.' Response: Admitted.

117. With regard to the July 27, 2017 Jinsheng Lin email, Mr. Chesney opined, "as a matter of GMP that the information in this e-mail could not be ignored; it needed to be aggressively evaluated by the so-called, quote-unquote, leaders as

soon as it was brought to their attention." (David Chesney Dep. Tr., 229:22-230:1, 230:9-16).

ZHP Defs.' Response: Denied. Mr. Chesney did not separately "opine[]" as Plaintiffs suggest, but simply agreed with counsel's statement in his deposition.

118. Mr. Chesney was questioned about an article he authored titled, "Executive Responsibility for Quality," in the book titled, "Quality Management Essentials, Expert Advice on Building a Compliant System." (David Chesney Dep. Tr., 233:22-234:10), which stated in part:

> Executive commitment to quality in the pharmaceutical industry is critical, not only to ensure continuing profitability of the company, but also for the safety and well-being of patients and to meet the needs of healthcare providers who prescribe and use pharmaceutical products every day.
>
> * * *
>
> For these reasons, quality assurance (QA) and GMP compliance may be viewed differently in the pharmaceutical industry than in those industries where a reputation for high quality drives sales. Quality assurance may be viewed as a 'cost of doing business' or an internal 'police department' issuing directives that delay or prevent product release. That viewpoint can result in a low priority being assigned to quality operations and resourcing, which can lead in turn to quality problems, regulatory difficulties, unnecessary expense, adverse publicity, lawsuits and investor disappointment. **All these consequences are preventable if executive managers understand the importance of the quality assurance function and treat it as a critical business operation**

> **just like other critical areas, such as strategic planning, financial management and others**.
>
> * * *
>
> In addition to the business benefits, health regulatory agencies around the world both require and expect top management to support a strong quality assurance function for their companies.

(David Chesney Dep. Tr., 234:24-235:9, 236:23-238:11).

ZHP Defs.' Response: Admitted.

119. Mr. Chesney confirmed that, "[t]op management would include, for example, the chairman of ZHP, Mr. Baohua Chen; he would fall within the context of top management." (David Chesney Dep. Tr., 238:7-10).

ZHP Defs.' Response: Admitted.

120. Mr. Chesney's article also lists, "Common Mistakes Executive Teams Make," including, "Emphasizing production quotas and market demands to the extent that quality problems are overlooked or regarded as unimportant - worst case, deliberate coverup of known quality problems through falsification of records." (David Chesney Dep. Tr., 247:24-248:14).

ZHP Defs.' Response: Admitted.

121. Mr. Chesney confirmed the executive responsibility for the failure to discharge quality duties:

> [T]here's a "growing consensus about the most critical quality management concepts. First among those is that executive management teams are the key to a company's

> ability to successfully meet quality standards on a consistent basis. Doing so is critical to proper clinical performance of the products of this industry and therefore, ultimately, to global public health."
>
> And you would agree that within ZHP, the ultimate responsibility lies with the executive management team, correct**?**
>
> * * *
>
> A. Yes, I would agree it applies to ZHP and everybody else in the industry.
>
> * * *
>
> The last paragraph of this article says, "Prudent management teams recognize this and support their quality units both philosophically and materially, with strong policies backed up by consistent actions, authority and resources. Failure to do so may have both serious business consequences for the company and potentially even personal consequences for individual executives."
>
> Again, that's a statement that you believe would hold true for ZHP and any company in this industry, right?
>
> A. Yes, any company in this industry.

(David Chesney Dep. Tr., 251:11-252:20 (discussing Ex. 57)).

ZHP Defs.' Response: Admitted with clarification. While Mr. Chesney agreed that the statement was accurate, he did not testify that ZHP failed to discharge quality duties.

The Discovery of the NDMA Contamination

122. The NDMA and NDEA contamination of ZHP's valsartan API and finished dose was first disclosed by ZHP to ZHP's customers, and the FDA and other

regulatory authorities, in June, 2018. This occurred after ZHP's API customer Novartis in Europe was provided valsartan API manufactured with the ZnCl2 process for evaluation for commercial purchase. Novartis tested the API and noted unexpected/unknown peaks on gas chromatography. Solvias, a third-party laboratory retained by Novartis, identified NDMA using gas chromatography and mass spectrometry ("GC-MS"). ZHP notified Prinston on June 6, 2018 that it believed the impurity causing unexpected/unknown peaks on gas chromatography was NDMA. Prinston notified the FDA as ZHP's agent 10 days later, on June 18, 2018. (ZHP00400220 (Ex. 58); ZHP00400281 (Ex. 59); ZHP00400236 (Ex. 60); PRINSTON00000022 (Ex. 61)).

ZHP Defs.' Response: Denied in part and admitted in part with clarification. According to the cited documents, Solvias only identified NDMA as a "tentative" finding, not a definitive one. (*See* ZHP00400281 at -288, -292, -297 (Pls.' SUMF Ex. 59).) While the ZHP Defendants admit the timing of when ZHP notified Prinston of the first report of NDMA in valsartan and when Prinston notified the FDA, they clarify that ZHP needed the time between these dates to confirm the suspected finding before alerting regulatory authorities. (*See, e.g.*, 3/10/21 Hai Wang Dep. 225:20-226:11 (Mr. Wang explaining that in his "professional experience you need a time to confirm that . . . the NDMA [is] present in the product using a validated analytical method," since "[y]ou cannot just . . . have a speculation over something

in the product and report it, it ha[s] to be confirmed"); 4/5/21 Eric Gu Dep. 222:4-223:24 (Mr. Gu explaining that he did not know exactly how long it took ZHP to "confirm it was NDMA" after the notification from Novartis, but that it took time because one must "get the reference data material from the market, . . . have the equipment to do such a job" and may "use different contract labs," and that ZHP "did so many experiments" and got "so many people . . . involved" in the confirmation process).

123. On May 22, 2018, an Irish subsidiary of Novartis asked ZHP to identify the source of various peaks seen on chromatography that Novartis had performed on valsartan API provided by ZHP to Novartis for evaluation for commercial sale. (Min Li 4/20/21 Dep. Tr., 198:13-204:2).

ZHP Defs.' Response: Admitted.

124. On June 5, 2018, Novartis communicated its preliminary assessment that the unidentified peaks indicated the presence of NDMA in the valsartan API. (Min Li 4/20/21 Dep. Tr., 198:13-204:2).

ZHP Defs.' Response: Admitted.

125. Solvias, the third-party laboratory hired by Novartis to test the API, used GC-MS technology to identify the NDMA. This technology had been available as of 2011 when the, "processes were being developed," and ZHP purchased that technology at least as of 2013. (Min Li 4/20/21 Dep. Tr., 204:3-206:13).

ZHP Defs.' Response: Admitted with clarification. While Dr. Li testified that ZHP purchased GC-MS hardware in 2013, ZHP did not do so with the intent to test valsartan for nitrosamines since ZHP was unaware of the potential formation of nitrosamine impurities at that time. Further, neither regulators nor ZHP had developed an analytical method to test valsartan for NDMA or NDEA prior to the 2018 recall; nor did they have reason to do so given that there was no expectation that these nitrosamines may be formed in valsartan. As Dr. Li explained, "GC-MS has been mostly . . . more like a research tool for QC residual solvent method" while "GC-FID method remains to be . . . the choice . . . of the method for controlling residual solvents." (4/20/21 Min Li Dep. 208:20-209:1; *see also* J. Kay et al., *Simultaneous quantitation of water and residual solvents in pharmaceuticals by rapid headspace gas chromatography with thermal conductivity detection (GC-TCD)*, J. Pharm Biomed Anal. 2021 Feb 5; 193:113796. Doj: 10.1016/j.jpba.2020.113796, https://pubmed.ncbi.nlm.nih.gov/33288344 ("Residual solvent determination in pharmaceuticals is most commonly performed using headspace capillary gas chromatography (GC) with flame ionization detection (FID).")).

Representations and Warranties
Regarding valsartan in the DMFs and ANDAs

126. According to the TEA DIR at 57-58 of 236:

- The DMF for the TEA process (without sodium nitrite quenching) was filed with USDMF registration number 23491. The date is not provided in the TEA DIR, but the filing date of January 22, 2010, is confirmed at PRINSTON00000005 (Ex. 62).

- The DMF for the TEA process with sodium nitrite quenching was filed in April 16, 2012. The USDMF registration number is not provided there, but is confirmed to be USDMF registration number 23491 at PRINSTON00000005.

- The DMF for the zinc chloride process was filed in December 2013 with USDMF registration number 23491.

ZHP Defs.' Response: Admitted.

127. The ANDAs filed by Prinston on September 13, 2012, and August 26, 2013, respectively, referenced USDMF registration number 23491, and the known list of impurities for that process, **not including NDMA or any other nitrosamine – because that was never approved or even raised as a possibility**.

(PRINSTON00000012	(Ex.	63);	ZHP01451842, -874	(Ex	64);
PRINBURY00058078	(Ex.	67);	PRINBURY00058083	(Ex.	68);
PRINSTON00037968, -972	(Ex.	69);	PRINSTON00183155	(Ex.	70);
PRINSTON00177677	(Ex.	71)).	The ANDAs also stated the valsartan was USP.		
(PRINSTON00000012	(Ex.	63);	ZHP01451842, -874	(Ex	64);
PRINBURY00058078	(Ex.	67);	PRINBURY00058083	(Ex.	68);

PRINSTON00037968 -972 (Ex. 69); PRINSTON00183155 (Ex. 70); PRINSTON00177677 (Ex. 71)).

ZHP Defs.' Response: Admitted with clarification. While the ANDAs filed by Prinston do not reference NDMA or any other nitrosamine, those impurities were not included in the ANDAs because no one in the scientific community had reason to believe they would be present in valsartan. (*See* Jucai Ge 5/26/22 Dep. 82:6-12 ("Prior to June 2018, [the ZHP Defendants] were not aware of . . . the existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process."); Afnan Rep. ¶ 145 ("If Plaintiffs[] [ ] were correct that any chemist should have known . . . that the TEA with quenching and Zinc Chloride processes were likely or even capable of causing nitrosamine formation, the expert chemists at the FDA would have been aware of these risks and flagged them in their valsartan ANDA reviews. There is no evidence anyone at the FDA had this concern prior to the identification of NDMA in valsartan in May 2018.").) Further, the ANDAs cited by Plaintiffs confirm that "[a]ll other impurities" besides known impurities would be controlled based on the USP monograph limit. (*See* Pls.' SUMF Ex. 67 at -081; *see also, e.g.*, Pls.' SUMF Ex. 64 at -848-850; Pls.' SUMF Ex. 69 at -972-975; Pls.' SUMF Ex. 70 at -157.)

128. On December 10, 2013 ZHP submitted its Technical Amendment to valsartan USP (Process II), DMF# 23491 to the FDA DMF Staff, for the change to the zinc chloride process, indicating in part the substitution of zinc chloride in step 4, and "in step 3 and step 4, DMF and MTBE are added to facilitate the process and will be successively removed." (ZHP01713711 (Ex. 72)).

ZHP Defs.' Response: Admitted.

129. The Amendment to Drug Master File dated December 10, 2013 states on page 11/16: **"There is no adverse change in qualitative and quantitative impurity profile, the process change/optimization does not impact the drug quality."** In addition, on page 15/16, "**The change does not affect the reproducibility of the production and the specification of intermediates & the final substance remains the same**." (PRINSTON00073102 (Ex. 73)).

ZHP Defs.' Response: Admitted.

130. Module 3.2.S.3.2 of the zinc chloride DMF dated November 10, 2013, titled Impurities, indicates on page 147 of 172 that the application of the "FDA draft guideline ***Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*** is applicable to the applications for existing active substances." The Module unequivocally states on pages 148-149 of 172 that all of the potential impurities were evaluated and**, NO "high potency genotoxic" N-nitroso- compounds are among the impurities, and the impurities pose "no**

genotoxic risk in valsartan." The same is stated with regard to residual solvents. (HUAHAI-US00007752 (Ex. 74)). The DMF also stated the valsartan was USP. (*Id.*).

ZHP Defs.' Response: Admitted with clarification. The section of the Module quoted identifies "[a]ll the potential organic impurities demonstrated in Valsartan" and then states that those particular identified impurities do not contain n-nitroso compounds. As noted above, neither NDMA nor NDEA was identified as a potential organic impurity in valsartan prior to 2018.

131. Module 3.2.S.3.2 of the TEA with sodium nitrite quenching DMF dated January 20, 2012, titled Impurities, indicates on page 108 of 133 that the application of the "FDA draft guideline ***Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*** is applicable to the applications for existing active substances." The Module unequivocally states on pages 109-110 of 133 that all of the potential impurities were evaluated and**, NO "high potency genotoxic" N-nitroso- compounds are among the impurities, and the impurities pose "no genotoxic risk in valsartan."** (PRINSTON00080011 (Ex. 75); PRINSTON00079747 (Ex. 76); PRINSTON00071532 (Ex. 77)). The DMF also stated the valsartan was USP. ((PRINSTON00080011 (Ex. 75); PRINSTON00079747 (Ex. 76); PRINSTON 00071532 (Ex. 77)).

ZHP Defs.' Response: Admitted with clarification. The section of the Module quoted identifies "[a]ll the potential organic impurities demonstrated in Valsartan" and then states that those particular identified impurities do not contain n-nitroso compounds. As noted above, neither NDMA nor NDEA was identified as a potential organic impurity in valsartan prior to 2018.

132. The ANDAs filed by Prinston referenced the DMF number 23491, and listed the drug formulations and impurities, with no mention of NDMA or NDEA. (PRINSTON00000012 (Ex. 63); ZHP01451842, -874 (Ex. 64); PRINBURY00058078 (Ex. 67); PRINBURY00058083 (Ex. 68); PRINSTON00037968, -972 (Ex. 69); PRINSTON00183155 (Ex. 70); PRINSTON00177677 (Ex 71)).

ZHP Defs.' Response: Admitted with clarification. While the ANDAs filed by Prinston do not reference NDMA or any other nitrosamine, those impurities were not included in the ANDAs because neither industry nor regulators had reason to believe they would be present in valsartan. (*See* Jucai Ge 5/26/22 Dep. 82:6-12 ("Prior to June 2018, [the ZHP Defendants] were not aware of . . . the existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process."); Afnan Rep. ¶ 145 ("If Plaintiffs[] [ ] were correct that any chemist should have known . . . that the TEA with quenching and Zinc Chloride processes were likely or even capable of causing nitrosamine formation, the expert chemists at the

FDA would have been aware of these risks and flagged them in their valsartan ANDA reviews. There is no evidence anyone at the FDA had this concern prior to the identification of NDMA in valsartan in May 2018.").) Further, the ANDAs cited by Plaintiffs confirm that "[a]ll other impurities" besides known impurities would be controlled based on the USP monograph limit. (*See* Pls.' SUMF Ex. 67 at -081; *see also, e.g.*, Pls.' SUMF Ex. 64 at -848-850; Pls.' SUMF Ex. 69 at -972-975; Pls.' SUMF Ex. 70 at -157.)

133. In connection with the change notification provided by ZHP to Prinston for the change to the zinc chloride process, Hai Wang confirmed that ZHP notified Prinston that there was "no adverse change in qualitative and quantitative impurity profile." (Hai Wang 3/11/21 Dep. Tr. 569:3-577:16 (Ex. 78)).

ZHP Defs.' Response: Admitted.

134. Mr. Dong confirmed that the December 10, 2013 DMF amendment for the zinc chloride process represented that "[t]here is no adverse change in qualitative and quantitative impurity profile, the process change/optimization does not impact the drug quality." Notwithstanding that representation, Mr. Dong admitted that the three validation batches for the zinc chloride process were addressed in the July 20, 2018 DIR for the zinc chloride process and shown to contain NDMA levels of 53.3, 51.6, and 76 ppm." (Peng Dong 3/31/21 Dep. Tr., 322:15-340:22).

ZHP Defs.' Response: Admitted with clarification. While the three validation batches for the zinc chloride process were shown to contain NDMA when tested in July 2018, the relevant authorities and industry did not have any understanding that NDMA could potentially form as part of the zinc chloride process for manufacturing valsartan API and therefore there was no scientific basis for either manufacturers or regulators to test for NDMA at the time that the December 10, 2013 DMF amendment for the zinc chloride process was submitted. (*See* Dong Dep. 340:3-22; *see also* August 2018 Gottlieb Statement at 4 (FDA noting in August 2018 that "NDMA's properties make it difficult to find," that "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it," and that "[b]efore [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process").)

ZHP's Valsartan Contained Probable Human Carcinogens and Presented an Unacceptable Carcinogenic Risk

135. Jucai Ge admitted that NDMA is a genotoxic impurity with mutagenic effects. (Jucai Ge 5/27/22 Dep. Tr., 173:11-20 (Ex. 123)).

ZHP Defs.' Response: Admitted with clarification. Ms. Ge stated that NDMA was a genotoxic impurity but noted that a substance that is genotoxic "[m]aybe . . . has certain effects such as DNA mutagenic." (5/27/22 Ge Dep. 173:11-

20.) Further, the FDA has noted that the trace NDMA impurity at the levels identified in recalled valsartan presented only a "very small" risk to patients. (*See* Ex. 65 to Defs.' SUMF.)

136. NDMA and NDEA are probable human carcinogens. (Min Li 4/20/2021 Dep. Tr., 102:5-8; Jun Du 5/27/21 Dep. Tr., 96:2-3; Hai Wang 3/10/21 Dep. Tr., 276:5-11, 321:16-22; John Iozzia 1/20/2021 Dep. Tr., 266:18-267:4).The World Health Organization's International Agency for Research on Cancer, the USP, and EPA all agree and classify NDMA and NDEA as probable human carcinogens. (Exs. 102-06). For example, the WHO states that "NDMA is highly likely to be carcinogenic to humans." (Ex. 103, p. 23).

ZHP Defs.' Response: Admitted with clarification. As the FDA explained, NDMA and NDEA are also present "in other ingested products," such as "charcoal grilled food items," "meats, dairy products," "vegetables" and even "water." (Ex. 65 to Defs.' SUMF.) Further, the trace NDMA impurity at the levels identified in recalled valsartan presented only a "very small" risk to patients. (*See* Ex. 65 to Defs.' SUMF.)

137. Eric Gu also agreed that NDMA was a probable human carcinogen. (Eric Gu 4/6/21 Dep. Tr., 360:8-374:12).

ZHP Defs.' Response: Admitted with clarification. In the cited testimony, Mr. Gu explained that ZHP "didn't know there were probable human carcinogens

like NDMA and NDEA" in valsartan in 2011, and also noted that he "do[es]n't know what [the phrase 'probable human carcinogen'] means" as used in letter shown to him in the deposition. (4/6/21 Eric Gu Dep. 366:8-19; 373:21-24.)

138. Published literature has confirmed that the use of the contaminated valsartan increased the risk of liver cancer, and that the increased risk was statistically significant. "A statistically significant association was found, however, between exposure to NDMA-contaminated valsartan and hepatic cancer." Gomm W, Röthlein C, Schüssel K, Brückner G, Schröder H, Heß S, Frötschl R, Broich K, Haenisch B. *N-Nitrosodimethylamine-Contaminated valsartan and the Risk of Cancer—A Longitudinal Cohort Study Based on German Health Insurance Data*. Dtsch Arztebl Int. 2021 May 28;118(21):357-362. doi: 10.3238/arztebl.m2021.0129. PMID: 34247699; PMCID: PMC8372009 (Ex. 92). This study also states, "The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities worldwide was necessary **in order to protect public health.**" (*Id.* at 4).

ZHP Defs.' Response: Denied in part. The authors of the cited study explain that, while their study can "state the existence of a statistical association" between valsartan with NDMA and hepatic cancer, "[c]ausality cannot be inferred" from those findings. (Pls.' SUMF Ex. 92 at 360.) Further, the study found "no association" between taking valsartan with NDMA and "the risk of cancer overall"; nor was any

statistically significant association found between taking valsartan with NDMA and increased risks of bladder, breast, colorectal, kidney, lung, malignant melanoma, pancreatic, prostate or uterine cancer. (*Id.* at 357, 361.)

139. Min Li confirmed that it would be unethical to perform a clinical study deliberately giving the contaminated valsartan/NDMA to human subjects due to the risk to health. (Min Li. 4/22/21 Dep. Tr., 685:11-687:4).

ZHP Defs.' Response: Denied. Min Li testified it would be unethical to conduct an experiment where humans are "given NDMA to see what happens" because of the "potential risk" to human health. He did not state or suggest that exposure to valsartan poses an actual risk to human health. (4/22/21 Li Dep. 685:11-686:12.)

140. Shortly after disclosing the contamination of its valsartan, ZHP filed a patent for an optimized manufacturing process to prevent nitrosamine contamination in valsartan, on July 17, 2018. The inventors were listed, including but not limited to Min Li, Peng Dong, Jinsheng Lin, and others. (Jucai Ge 5/27/22 Dep. Tr., 159:12--161:10).

ZHP Defs.' Response: Admitted.

141. The July 17, 2018 patent, "correctly referred to NDMA as a **highly toxic impurity**..." (Jucai Ge 5/27/22 Dep. Tr., 159:12-161:20).

ZHP Defs.' Response: Denied. Plaintiffs take the deposition testimony out of context. Ms. Ge only testified that the referenced patent document contains the quote listed in Paragraph 141, not that the document is correct in referring to NDMA as a highly toxic impurity. (5/27/22 Jucai Ge Dep. 161:18-20 (Pls.' SUMF Ex. 123).) As the FDA explained, NDMA and NDEA are also present "in other ingested products," such as "charcoal grilled food items," "meats, dairy products," "vegetables" and even "water," and the trace NDMA impurity at the levels identified in recalled valsartan presented only a "very small" risk to patients. (*See* Ex. 65 to Defs.' SUMF.)

142. Ms. Ge also agreed the patent confirmed that, "These changes to the manufacturing process were necessary to ensure the valsartan medication safety." (Jucai Ge 5/27/22 Dep. Tr., 159:12-162:5).

ZHP Defs.' Response: Denied. Ms. Ge was not offering agreement that the patent "confirmed" those changes were necessary to ensure valsartan was safe. Instead, she was merely agreeing that those words appeared on the page of the patent that counsel was reading from:

> Q. At the very end of that sentence, it also indicated that these changes to the manufacturing process were necessary to ensure the valsartan medication safety, correct?
>
> A. Well, ***I see the wording in this paragraph***, "thereby ensuring the valsartan medication safety."

(5/27/22 Ge Dep. 161:22-162:5 (emphasis added).)

Further, Ms. Ge emphatically disagreed with Plaintiffs' counsel that "having NDMA in ZHP's valsartan increases the risk for persons taking those pills to develop cancer." (*Id.* 162:8-16.)

143. Jun Du confirmed that the press releases issued by both Prinston and Solco announcing the recall of the valsartan containing the NDMA impurity stated in part that the recall was due to, "**an unacceptable carcinogenic risk to the intended patient population**." (Jun Du 5/27/21 Dep. Tr., 91:17-94:22). The notices recalled all valsartan products within expiry. (SOLCO00024231 (Ex. 118); SOLCO00024226 (Ex. 119)).

ZHP Defs.' Response: Denied. Mr. Du never confirmed that the recall notices stated that the recall was "due to" an unacceptable carcinogenic risk; nor does the quoted sentence from the recall notice state that an "unacceptable carcinogenic risk" was the "reason" for the recall:

> Q. Looking now at the italicized language just above the table in the middle of the page, this states in part: "The exposure to the impurity n-nitroso-dimethylamine (NDMA) that was detected in valsartan product line presents an unacceptable carcinogenic risk to the intended patient population."
>
> That's the reason for the recall, correct?
>
> A. We included this sentence according to FDA's requirement.

(5/27/21 Du Dep. 94:11-22.)

The reason for the recall is stated clearly in both recall notices cited by Plaintiffs: "This product recall is due to the detection of a trace amount of an unexpected impurity, N-nitrosodimethylamine (NDMA)." (Pls.' SUMF Ex. 119; *see also* Pls.' SUMF Ex. 118 (same).)

143.5. Jie Wang confirmed that ZHP was not supposed to release a batch for sale, "if the manufacturing process produced API that contained a genotoxic impurity," and/or if the product did not comply with cGMPs and the related regulations. (Jie Wang 5/19/21 Dep. Tr., 279:7-282:8, 288:14-20 (Ex. 114)).

ZHP Defs.' Response: Admitted with clarification. Mr. Wang did not testify that ZHP failed to comply with CGMPs and the relevant regulations, but was simply answering hypothetical questions about what ZHP should have done if it had known that its API contained a genotoxic impurity. As explained above, ZHP was not aware of NDMA or NDEA in its API and does not agree that it failed to comply with CGMP. (*See supra* ¶¶ 57, 60, 63.)

144. The corporate representatives of the pharmacies also confirmed that they would not have sold the valsartan if they knew that it was adulterated due to the unacceptable contamination. Own McMahon, Rite Aid's Vice President of Pharmaceutical Purchasing confirmed that "Rite Aid could not ... knowingly sell adulterated drug products." (Owen McMahon 9/23/21 Dep. Tr., 52:13-16, 51:17-18,

51:22-52:6, 52:20-23, 65:10-13, 65:15-18, 65:20-22, 65:25-66:5, 137:8-11 (Ex. 93)). John Holderman, CVS's Senior Director at CVS Health for Pharmacy Merchandising testified that "CVS would not knowingly sell" adulterated or misbranded products. (John Holderman 10/1/2021 Dep. Tr., 113:3-5, 113:7-8, 122:2-5, 122:11-12, 158:20-22, 195:4-5 (Ex. 94)). Humana's Cesar Cedeno confirmed that it can't sell drugs that are adulterated, like valsartan that's contaminated with NDMA." (Cesar Cedeno 9/27/21 Dep. Tr., 28:1-3, 28:6, 28:25:20-23, 26:2-3, 28:10-11, 28:13, 30:25-31:5, 31:8-9, 31:14-15, 31:20-21 (Ex. 95)). Walgreen's Director of Pharmacy Quality Assurance and Patient Safety, Catherine Stimmel, agreed that "a product considered adulterated can't be sold." (Catherine Stimmel 9/20/2021 Dep. Tr., 32:4-6, 32:10, 32:17-19, 32:24-33:2, 33:46, 33:9, 76:12-19, 77:5-11, 77:13-15, 78:8-11, 78:14 (Ex. 96).

ZHP Defs.' Response: Admitted with clarification. There has been no finding that ZHP's API was adulterated or misbranded at the time that it was sold, and the FDA's Warning Letter does not suggest otherwise. Also see response to Paragraph 47.

Warranties and Representations

145. **ZHP represented at all times that the valsartan, "released and distributed in the US at all times met appropriate standards reviewed and approved by the FDA. Since the product had the USP designations, or the USP**

specification, the requirement has been met." (Hai Wang 3/10/21 Dep. Tr. 62:18--63:7). The valsartan's labelling explicitly stated it was USP and included the National Drug Codes (NDCs) representing the inclusion of valsartan at specific dosages. (PRINSTON00035229 (Ex. 97); PRINSTON00065545 (Ex. 98)). These NDCS were listed in the National Drug Code Directory referencing ANDAs held by Prinston. (https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory). The valsartan's prescribing information explicitly stated it was USP and FDA approved. (PRINSTON00032437 (Ex. 99); PRINSTON00248665 (Ex. 100)).

ZHP Defs.' Response: Denied. Plaintiffs are incorrect that ZHP represented that valsartan met the appropriate standards reviewed and approved by the FDA and met USP requirements. The cited testimony from Mr. Wang supports, at most, that "Prinston and Solco" may have made representations that finished dose valsartan complied with applicable regulatory requirements. (3/10/21 Hai Wang Dep. 62:18-7.) Moreover, both the FDA and USP standards allow the presence of non-identified impurities below a certain threshold (*see supra* ZHP Defendants' response to ¶ 36), and Plaintiffs have not established that the NDMA or NDEA present in either the valsartan API or the VCDs ever exceeded that threshold.

146. **The use of the USP designation was a representation "to anybody who is buying it or using it," that "all the USP requirements were applied."** (Hai Wang 3/10/21 Dep. Tr. 63:9-18).

ZHP Defs.' Response: Admitted that Mr. Wang provided this testimony with clarification that Mr. Wang cannot speak on behalf of purchasers or consumers and that ZHP did not make such representations to purchasers or consumers. Moreover, the USP allows the presence of non-identified impurities below a certain threshold (*see supra* ZHP Defendants' response to ¶ 36), and Plaintiffs have not established that the NDMA or NDEA present in either the valsartan API or the VCDs ever exceeded that threshold.

146.5. ZHP sold its API designated as "valsartan USDMF Grade API," which meant that the product is what they "submitted with the US FDA under our DMF." (Jie Wang 5/19/21 Dep. Tr., 184:22-186:11 (Ex. 114)).

ZHP Defs.' Response: Denied in part. While ZHP did sell some of its API as USDMF Grade, ZHP also sold API outside the United States under a different standard. (5/19/21 Jie Wang Dep. 186:1-21 (Pls.' SUMF Ex. 114).)

147. ZHP always represented that the valsartan it sold was Orange Book AB rated, meaning, **"it's the therapeutic equivalent of the brand name product...it has the same quality and purity as the brand name product...the drug was manufactured in compliance with current good manufacturing practice**

regulations." (Hai Wang 3/10/21 Dep. Tr. 82:4-83:22, 84:2-5, 84:19, 84:22-85:10). For the Orange Book, "[t]he main criterion for the inclusion of any product is that the product is the subject of an application with an approval." (*Orange Book Preface*, https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface (Ex. 107, p. 1)). The Orange Book's "[a]pproved drug products are considered to be therapeutic equivalents." (*Id.* at 4; *see also* 21 C.F.R. § 314.3). More specifically:

> FDA classifies as therapeutically equivalent those drug products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (b) **meet compendial or other applicable standards of strength, quality, purity, and identity**; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; **(4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations**.

(Ex. 107, p. 4 (emphasis added)). Additionally, the valsartan was listed in the Orange Book as AB rated to the RLD Diovan. (Ex. 7, p. 33, 35).

ZHP Defs.' Response: Denied in part. While Plaintiffs accurately quote the Orange Book, the cited portion of Mr. Wang's testimony does not suggest that "ZHP always represented that the valsartan it sold was Orange Book AB rated." The

testimony only states that "Prinston and Solco have always represented" to their customers that their valsartan products were the therapeutic equivalent of the brand name product. (3/10/21 Hai Wang Dep. 85:5-10.)

148. In other words, ZHP represented to all of its customers, "that they were being sold valsartan that was compliant with the current USP and Orange Book standards...the product is approved by the FDA. It meets all the FDA's requirement and specifications." (Hai Wang 3/10/21 Dep. Tr. 89:7-16).

ZHP Defs.' Response: Denied. The cited deposition testimony does not state that "ZHP represented" such information to its customers. At most, the testimony suggests that "Prinston and Solco" made representations that finished dose valsartan complied with applicable regulatory requirements. (3/10/21 Hai Wang Dep. 87:7-89:16.) Indeed, it is not clear that Mr. Wang even adopted the assertion of Plaintiffs' counsel regarding the USP and Orange Book. Specifically, Mr. Wang only stated that the finished dose valsartan met ***FDA*** requirements:

> Would you agree with me that
> all of the customers listed here would have
> been told by your company that they were
> being sold valsartan that was compliant with
> the current USP and Orange Book standards?
> [Objection Omitted.]
> A. Yeah, the product is approved
> by the FDA. It meets all the FDA's
> requirement and specifications.

(*Id.* 89:8-16.)

149. The Prinston website represents that the products sold by Prinston (manufactured by ZHP), "are manufactured in state-of-the-art GMP facilities using the highest quality assurance standards that meet the FDA regulatory requirements." (Hai Wang 3/10/21 Dep. Tr. 37:3-11).

ZHP Defs.' Response: Admitted that the content of the ZHP website speaks for itself.

150. Those representations have been made to all of Prinston's customers and it was expected that since 2012, "**anybody buying products from Prinston**," **would, "expect that those products were manufactured in state-of-the-art GMP facilities using the highest quality assurance standards that meet the FDA regulatory requirements.**" (Hai Wang 3/10/21 Dep. Tr. 37:12-38:6).

ZHP Defs.' Response: Denied. The cited testimony does not establish that the referenced statements were made to all of Prinston's customers. At most, Mr. Wang speculatively stated that he "believe[d]" such a statement was provided to customers and that "he" subjectively expected customers to expect Prinston products were produced in certain facilities. (3/10/21 Hai Wang Dep. 37:12-38:6.)

151. At all times that Solco has, "distributed products for Prinston...it has represented to its customers that the products were high quality..." and that, "Our products are manufactured in state-of-the-art GMP facilities in the US and overseas using the highest quality assurance standards that meet the FDA regulatory

requirements." (Hai Wang 3/10/21 Dep. Tr. 42:19-43:8, 43:10-17, 44:1-4, 44:7--45:6).

ZHP Defs.' Response: Admitted.

152. At all times it has always been understood, "that when people buy products from Prinston and Solco that they trust that the products are what they're supposed to be and that they were manufactured in the highest quality way." (Hai Wang 3/10/21 Dep. Tr. 47:5-13).

ZHP Defs.' Response: Denied in part. Mr. Wang testified that he subjectively "understood" that, when people buy products from Prinston and Solco, they trust that the products "are what they're supposed to be and that they were manufactured in the highest quality way," not that such a fact was understood by others. (*See* 3/10/21 Hai Wang Dep. 47:5-13.)

153. John Iozzia, Director of Marketing for the API division of Huahai, US, confirmed that ZHP had internally recognized that CGMPs were applicable throughout the lifecycle of the products it sold. (John Iozzia 1/20/21 Dep. Tr. 86:10--90:11 (Ex. 79)).

ZHP Defs.' Response: Denied. The cited testimony states that "quality practices" are applicable through the lifecycle of the products Huahai sold. (1/20/21 Iozzia Dep. 88:13-20 (Pls.' SUMF Ex. 79).)

154. Mr. Iozzia discussed a marketing PowerPoint that represented, "Huahai commits that quality is our life. Employs quality practices during the whole life cycle of products. Meets and exceeds the regulatory agency's requirement...Huahai uses high quality standard and adopts continuous quality improvement and innovation strategy to ensure strict scientific and systematic quality management system," and agreed that, "**this is something that your company has always represented to other companies and the public, that this is how your company conducts its quality operations...**". (John Iozzia 1/20/21 Dep. Tr. 86:10-90:11).

ZHP Defs.' Response: Admitted.

154.5. The quality agreements between ZHP and Teva/Torrent represented, among other things, that the equipment and facilities were "in compliance with the current EU and/or FDA regulatory standards and guidance documents," each batch would be manufactured, "in accordance with the cGMP and legal and regulatory requirements," and ZHP would comply with ICH Q7 – Good Manufacturing Practices for Active Pharmaceutical Agents. (Jie Wang 5/19/21 Dep. Tr., 269:19-273:23, 274:10-277:14, 278:2-279:4, 286:2-13, 288:21-289:5 (Ex. 114)). ZHP also represented that "The reagents, intermediates and impurities including Azide susceptible of generating genotoxic impurities have been taken into account, no genotoxic impurities are present in the substance, and it comply with TTC rule concluded an acceptable limit of 4.7 ppm based on the maximum dosage for

valsartan 320 mg/day." (TORRENT-MDL2875-00003964 (Ex. 115); TORRENT-MDL2875-00002185 (Ex. 116)).

ZHP Defs.' Response: Denied in part. The quoted testimony and document do not say "legal and regulatory requirements." The correct wording is "legal and registration requirements." (5/19/21 Jie Wang Dep. 276:24-277:9.)

The Warranties Were Breached

155. ZHP's recall notices confirmed that the NDMA contamination constituted, "an unacceptable carcinogenic risk to the intended patient population." (Hai Wang 3/10/21 Dep. Tr. 274:19-283:19).

ZHP Defs.' Response: Denied in part. As explained by Mr. Wang, the statement quoted by Plaintiffs was a "mandate[] of the FDA," which the ZHP Defendants do "not necessarily agree with." (3/10/21 Hai Wang Dep. 278:12-279:1; *see also* 5/27/22 Ge Dep. 188:21-190:7.)

156. Hai Wang testified that "if that spec has been established, and the product has NDMA level exceeding that 96-nanogram part, the product ... [c]ould not be sold because it's not meeting spec, period." (Hai Wang 3/10/2021 Dep. Tr. 301:6-13).

ZHP Defs.' Response: Admitted with clarification. The 96 nanogram standard referenced is the interim acceptable intake limit set by the FDA post-recall. (*See* FDA February 28, 2019 Announcement at 8-9 (Defs.' SUMF Ex. 69).) There

was no intake limit pre-recall because no one expected NDMA or NDEA formation in valsartan. (*See* August 2018 Gottlieb Statement at 4 (FDA noting in August 2018 that: (1) "NDMA's properties make it difficult to find," (2) "[b]ecause it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it," and (3) "[b]efore [the FDA] undertook [an] analysis [following the discovery of NDMA in ZHP's valsartan API], neither regulators nor industry fully understood how NDMA could form during this process").)

157. Hai Wang confirmed that "No wants to have NDMA," in valsartan. (Hai Wang 3/10/21 Dep. Tr. 325:18-326:1).

ZHP Defs.' Response: Admitted.

158. Eric Gu of Shanghai Syncores/ZHP, which developed the zinc chloride process in the laboratory confirmed that if the NDMA and NDEA in the valsartan API manufactured with the zinc chloride and TEA process with sodium nitrite quenching had been known the drug products could not have been sold: "If we known that, it shouldn't be sell on the market." (Eric Gu 4/6/21 Dep. Tr. 391:12--394:7, 395:10-397:10).

ZHP Defs.' Response: Admitted with clarification. Valsartan API that contains NDMA or NDEA could not be sold on the market today if the amounts were in excess of the limits set by the FDA following the 2018 recall.

159. Jucai Ge confirmed, "From the regulatory point of view, ZHP, our company, agrees that to FDA the level of NDMA was unacceptable...the pills with such a level would be unacceptable." (Jucai Ge 5/27/22 Dep. Tr., 188:21-189:8, 190:19-191:3).

ZHP Defs.' Response: Admitted.

160. **Mr. Gu confirmed that, "If we knew, okay, there's NDMA in the valsartan, you know, ZHP wouldn't sell that,"** and as a matter of evaluation of the health or safety issues at the levels of NDMA shown on the testing, ZHP stopped selling and recalled all the pills containing NDMA. (4/6/21, 391:12-394:7).

ZHP Defs.' Response: Admitted.

161. **Mr. Gu confirmed the same with regard to the TEA process with sodium nitrite quenching, "If we known that, it shouldn't be sell on the market," for the same reasons as with the zinc chloride process.** (4/6/21, 395:10-397:10).

ZHP Defs.' Response: Admitted.

162. John Iozzia, Director of Marketing for the API division of Huahai, US, testified that the API sold by ZHP was not, "supposed to contain dangerous unintended impurities...If it was determined that there was such an issue with the product, then it would not be a quality product." (John Iozzia 1/20/21 Dep. Tr. 21:1-22:9, 79:12-80:2).

ZHP Defs.' Response: Admitted with clarification. While Mr. Iozzia testified as stated, Mr. Iozzia did not testify that anyone at Huahai was aware that valsartan API contained any impurities prior to the recall.

163. Mr. Iozzia testified that there was not, "any customer you're aware of that would purchase valsartan API if they knew that it was either contaminated or it might be contaminated and that could not be ruled out." (John Iozzia 1/20/21 Dep. Tr., 294:2-14).

ZHP Defs.' Response: Admitted that Mr. Iozzia agreed with the quoted statement made by Plaintiffs' counsel but denied that Mr. Iozzia can speak on behalf of valsartan purchasers. The ZHP Defendants also deny that all valsartan API was contaminated.

163.1. Min Li admitted that "NDMA is highly likely to be carcinogenic to humans," as concluded in a 2002 peer reviewed WHO publication cited by ZHP in its own Deviation Investigation Report, stating, "highly likely, you know, is probable." Dr. Li then agreed that ZHP stopped selling the contaminated valsartan because it was deemed "highly likely to be carcinogenic to humans," and confirmed that, "At the levels of contamination that we've gone through in this deposition, it would be unacceptable and, using your word, unethical to sell valsartan with those levels of NDMA contamination [documented by ZHP]," if that was knowingly done. (Min Li 4/22/21 Dep. Tr., 696:3-697:4; 699:24-700:15).

ZHP Defs.' Response: Denied in part. While the quoted language in Paragraph 163 appears in Dr. Li's deposition testimony, Dr. Li did not testify that "ZHP stopped selling the contaminated valsartan because it was deemed 'highly likely to be carcinogenic in humans.'" The ZHP Defendants voluntarily recalled valsartan "due to the detection of a trace amount of an unexpected impurity, N-nitrosodimethylamine (NDMA)." (SOLCO00000173 (Defs.' SUMF Ex. 2).) The FDA "estimated that if 8,000 people took the highest valsartan dose (320 mg) from NDMA-affected medicines daily for four years (the amount of time we believed the affected products had been on the U.S. market), there may be one additional case of cancer over the lifetimes of these 8,000 people beyond the average cancer rate among Americans. This estimate represented the highest possible level of NDMA exposure. It was a measure of the risk under the most extreme circumstances. Most patients who were exposed to the impurity through the use of valsartan received less exposure than this worst-case scenario." (August 2018 Gottlieb Statement at 4.) Similarly, the FDA stated that it "estimate[s] that if 18,000 people took valsartan at the highest dose (320 mg) containing NDEA from recalled batches daily for four years, there may be one additional case of cancer over the lifetime of these 18,000 people." (TPP Trial Defs.' SUMF Ex. 71 (FDA, Laboratory Analysis of valsartan Products).)

163.2. At all times, ZHP had, "a responsibility to be truthful with its customers," and ZHP was obligated to disclose its knowledge about the NDMA contamination of its valsartan as discussed in the July 27, 2017 email. (Jie Wang 5/18/21 Dep. Tr., 86:21-87:1 (Ex. 117); 5/19/21 Dep. Tr., 292:13-294:21 (Ex. 114)).

ZHP Defs.' Response: Denied in part. While ZHP had a responsibility to be truthful to its customers, the cited July 27, 2017 email does not demonstrate that ZHP had "knowledge about the NDMA contamination" in valsartan API in 2017. As Jucai Ge explained, "if you look into the context of [the July 27, 2017] e-mail, you can tell that at that time [Dr. Lin] was trying to make a comparison between NDMA and Impurity K and the impurity found in the technical improvement of irbesartan, since they were all nitroso compounds, and he was merely trying to make a toxicology comparison." (Jucai Ge 5/26/22 Dep. 92:8-15.) Ms. Ge also clarified that, "[p]rior to June 2018, [the ZHP Defendants] were not aware of . . . the existence of the NDMA in the valsartan that [they] manufactured using the zinc chloride process." (Jucai Ge 5/26/22 Dep. 82:6-12.)

Teva and Torrent Purchased and Utilized ZHP's Contaminated Valsartan

164. ZHP sold valsartan API manufactured with the zinc chloride process to Teva which then utilized that API in the manufacture of Teva finished dose valsartan for sale in the United States. (PRINSTON00000001-46 (Exs. 80, 62, 63, 60);

ZHP02364173 (Ex. 15); Teva 230 (Ex. 81); Michelle Osmian 5/06/2021 Dep. Tr. 33:2-236:24; 239:7-240:2 (Ex. 82)).

ZHP Defs.' Response: Admitted.

165. In a September 13, 2018 letter from Teva to ZHP, Teva stated in part, (Teva-MDL2875-00324735 (Ex. 83)):

> By letter dated June 20, 2018, Teva received formal notification from Huahai, indicating a previously unknown impurity was identified that may have genotoxic potential with respect to valsartan API. This notification was followed by a subsequent notification letter dated June 25, 2018, indicating that based on a preliminary investigation, the previously unknown impurity was suspected to be NDMA, and was likely to be process-related.

ZHP Defs.' Response: Admitted.

166. Valsartan API manufactured with the TEA process with sodium nitrite quenching was sold to Torrent and then utilized by Torrent in the manufacture of Torrent finished dose valsartan for sale in the United States. (TORRENT-MDL2875-00072650 (Ex. 84); Sushil Jaiswal Dep. Tr. 6/04/20211, 67:21-24, 68:1-7 (Ex. 85)).

ZHP Defs.' Response: Admitted.

167. Torrent unequivocally notified ZHP that it never would have purchased or used the valsartan API manufactured with the TEA process with sodium nitrite quenching if it had known of the NDEA and NDMA contamination, having relied

on the DMF and ZHP's inaccurate representations as to genotoxic impurities, which did not disclose the NDEA or NDMA. In the February 13, 2019 letter from Makesh Agravad of Torrent to "Mr. Zenson, ye" of ZHP, Torrent stated in part:

> As notified in Huahai in its various communications to Torrent starting from 20.06.2018, it is now clear **that contrary to Huahai's declarations regarding the absence of genotoxic impurities, the API supplied by Huahai to Torrent did contain certain genotoxic impurities, namely, N-Nitroso-dimethylamine ("NDMA") and N-Nitrosodiethylamine ("NDEA") on account of the manufacturing process employed by Huahai and thus there has been a clear breach of the representations and warranties provided by Huahai to Torrent.** It is also clear that these impurities were present in all batches of the API supplied by Huahai. **Since NDMA and NDEA have been classified as a probable human carcinogenic, Torrent had to recall all its existing batches of formulations containing valsartan from the various jurisdictions, including, United States and stop any further sale.**

(ZHP02592303, Paragraph 5 (Ex. 86)).

ZHP Defs.' Response: Denied. The cited letter, at most, states that Torrent's API purchases were "premised" on the cited facts, not that Torrent "unequivocally notified ZHP that it never would have purchased or used the valsartan API manufactured with the TEA process with sodium nitrite quenching." (*See* Pls.' SUMF Ex. 86 at -303-304.)

The NDMA/NDEA Contamination of ZHP's API Could Have Been Easily Prevented

168. ZHP established that the zinc chloride process could have been "optimized" to prevent NDMA contamination of the product by extracting the product prior to quenching the sodium azide, "any formation of NDMA will not be carried over into the product." Moreover, this simple step would not have required any change to the manufacturing process, **"This approach can be done without any change of manufacturing process."** (July 1, 2018 Investigation of the Source of this Impurity, NDMA, ZHP01495188 (Ex. 87)).

ZHP Defs.' Response: Denied in part. While Plaintiffs have correctly quoted the document, the ZHP Defendants object to Plaintiffs' characterization of removing the product prior to quenching as a "simple step," which does not appear in the document.

169. ZHP also stated that the process could have been optimized in the same way in the TEA process with sodium nitrite quenching, stating in part: "After optimization, the ROS remains the same, the product in valsartan Crude Step (Step 4) is separated before the addition of NaNO2 (and the subsequent addition of HCl)...Therefore, the product in the organic phase **has no chance to be contaminated by NDMA."** (TEA DIR at 29-35 of 236 (Ex. 10)).

ZHP Defs.' Response: Admitted.

170. Accordingly, in July 2018 (after disclosure of the NDMA contamination) ZHP submitted an Amendment to Drug Master File, in an attempt to modify the zinc chloride process to extract the product before quenching the sodium azide, in order to eliminate the risk of NDMA contamination. (ZHP00097775, ZHP00097777 (Exs. 88, 89)). Section 2 indicates "The purpose of this technical amendment is to provide the quality control of newly identified genotoxic impurity N-Nitrosodimethylamine (NDMA) in the specification of final drug substance." The optimization is described (at ZHP00097782 (Ex. 89)) as, "the product in Step 4 will be separated before the addition of NaNO2 (and the subsequent addition of HCl)....Since there is no chance for residual dimethylamine to react with HNO2 (NaNO2/HCl) in the presence of the product, there will be no chance for NDMA to be produced in this optimized process [hereafter referred to as Process (separated quenching)]. **In the optimized process, the sequence and the principles of the chemical reactions have no change, and the process remains the same, as well as the crystallization step leading to the final drug substance. Hence, this is a very minor change from a drug substance process perspective." (ZHP00097775, ZHP00097777).**

ZHP Defs.' Response: Admitted.

Dated: January 22, 2024 Respectfully submitted,

By: */s/ Jessica Davidson*
SKADDEN, ARPS, SLATE, MEAGHER &

FLOM LLP
Jessica Davidson (NY Bar No. 6034748)
Liaison Counsel for Manufacturer Defendants

Allison M. Brown (NJ Bar No. 044992012)
One Manhattan West
New York, New York 10001
Phone: (212) 735-3222
Fax: (917) 777-3222
jessica.davidson@skadden.com
allison.brown@skadden.com

Nina R. Rose (DC Bar No. 975927)
1440 New York Avenue, N.W.
Washington, D.C. 20005
Phone: (202) 371-7000
Fax: (202) 661-0525
nina.rose@skadden.com

Attorneys for Zhejiang Huahai Pharmaceutical Co., Ltd., Huahai U.S., Inc., Prinston Pharmaceutical Inc., and Solco Healthcare U.S., LLC

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on January 22, 2024, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system, which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ *Jessica Davidson*

Jessica Davidson (NY Bar No. 6034748)